Official Title of Study:

A Phase 3 Randomized Clinical Trial of Nivolumab Alone, Nivolumab in Combination With Ipilimumab, or Investigator's Choice Chemotherapy in Participants With Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

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CLINICAL PROTOCOL CA2098HW

A Phase 3 Randomized Clinical Trial of Nivolumab alone, Nivolumab in Combination with Ipilimumab, or Investigator's Choice Chemotherapy in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

(CheckMate 8HW: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 8HW)

Protocol Amendment: 10

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 10	01-Jul-2024	Due to the delay of progression-free survival (PFS) events for the comparison of Arms B vs A all lines, the pre-planned, study-wise final analysis for overall survival (OS), planned to occur around 5-years from the first participant randomized (which is around Aug-2024), is no longer feasible because it will deviate from the study testing strategy. In order to maintain the testing strategy in the pre-planned analysis around Aug-2024, the study-wise final analysis for OS at the 5-year mark is removed and an interim analysis of PFS B vs A in all lines is added to occur at this time. If PFS B vs A in all lines meets its pre-specified statistical significance in this interim analysis (IA), the secondary endpoints including OS (IA) are allowed to be tested following the testing strategy. PFS final analysis time is updated to occur at approximately the 2-year minimum follow-up of all randomized participants. Overall survival final analysis time is updated to occur at approximately the 3-year minimum follow-up of all randomized participants.
Protocol Amendment 09	01-Jun-2023	Given the heterogeneity of patient populations (first-line [1L] and all lines) and different mode of action of study drugs (chemotherapy and immuno-oncology [I-O] therapy) the progression-free survival (PFS) event accumulation may not align for the 2 primary endpoints (PFS Arm B vs Arm C 1L and PFS Arm B vs Arm A all lines). The protocol is being amended to allow the option to trigger the interim analysis (IA) for each primary endpoint independently if the projected number of PFS events do not occur in close proximity to each other. In this case separate database locks (DBLs) may be conducted for IA of each primary endpoint.
Administrative Letter 04	05-Jan-2023	The purpose of this administrative letter is to inform you of updated language corresponding to the collection of plasma samples (for ctDNA analysis) to correct a typo in the protocol.
Protocol Amendment 08	04-Aug-2022	The purpose of this amendment is to specify that the data monitoring committee (DMC) will be utilized for the assessment of the study interim data and it will be providing recommendation to Bristol-Myers Squibb (BMS) on the next steps with regards to the study conduct.
Protocol Amendment 07	10-May-2022	The main objective of Protocol Amendment 07 was to update the statistical analyses schedule to reflect new enrollment timelines for Part 2. In addition, the projection of the number of randomized participants based on local mismatch repair deficient/microsatellite instability high (dMMR/MSI-H) status has been revised to reflect higher than initially assumed discordance rate between central and local dMMR/MSI-H testing results. Other changes made to comply with Health Authorities' requests to include additional safety language around oxaliplatin use and clarification on contraception requirements for study participants.

Document	Date of Issue	Summary of Change
Protocol Amendment 06	01-Oct-2021	The protocol was revised to update the statistical testing strategy for study primary endpoints. Frequency of the tumor assessments has been reduced after the first 2 years from randomization. In addition, other minor clarifying updates were included.
Administrative Letter 03	09-Jun-2021	Study acknowledgement page was corrected.
Administrative Letter 02	11-Jan-2021	Noted changes to HIV testing for participants in Italy.
Protocol Amendment 05	18-Nov-2020	The protocol was updated to include dose modification criteria for immuno-oncology (I-O) therapy and I-O-related AE management algorithms based on version 5 of common terminology criteria (CTCAE v5). Program level updates were incorporated, including new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) study requirements, male contraception requirements in connection with I-O therapy. Additional safety requirements for oxaliplatin included.
Revised Protocol 04	17-Jul-2020	The study design was amended to expand enrollment of participants who have not received prior therapy for metastatic disease. Second primary endpoint (comparison of PFS between nivolumab plus ipilimumab arm and chemotherapy arm in participants who have not received prior therapy) was also added. Updated study rationale to reflect recent internal and external data in dMMR/MSI-H mCRC patients. Modified objectives and statistical analyses. Additional editorial or formatting changes, where appropriate were made.
Revised Protocol 03	28-Mar-2019	The study design was amended to include the standard of care (SOC) Arm that will allow for comparison of efficacy and safety of immunotherapy vs chemotherapy in 1L and 2L settings in a prospective randomized study.
Revised Protocol 02	20-Dec-2018	Modified to become a randomized controlled trial (RCT) to compare nivolumab monotherapy to combination (nivolumab +ipilimumab) therapy in participants with and without prior treatment for metastatic disease.
Revised Protocol 01	16-May-2018	Modified inclusion criteria in order to extend eligibility to the subgroup of patients who received first line chemotherapy as a triplet chemotherapy combination (FOLFOXIRI).
Original Protocol	03-Apr-2018	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 10:

Due to the delay of progression-free survival (PFS) events for the comparison of Arms B vs A all lines, the pre-planned, study-wise final analysis for overall survival (OS), planned to occur around 5-years from the first participant randomized (which is around Aug-2024), is no longer feasible because it will deviate from the study testing strategy. In order to maintain the testing strategy in the pre-planned analysis around Aug-2024, the study-wise final analysis for OS at the 5-year mark is removed and an interim analysis of PFS B vs A in all lines is added to occur at this time. If PFS B vs A in all lines meets its pre-specified statistical significance in this interim analysis (IA), the secondary endpoints including OS (IA) are allowed to be tested following the testing strategy. PFS final analysis time is updated to occur at approximately the 2-year minimum follow-up of all randomized participants. Overall survival final analysis time is updated to occur at approximately the 3-year minimum follow-up of all randomized participants.

The protocol synopsis was updated to reflect changes in the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated "EUDRACT Number" to "EU CT Number."	The term "EudraCT" is obsolete, as it refers to the previous legislation shortening the number per Clinical Trial Regulation (CTR) minimum requirements.
	Updated the European Union (EU) Clinical Trial (CT) number.	
Section 5.1: Overall Design Figure 5.1-1: Study Design Schematic	Updated to include that Part 2 randomization was completed in Apr-2023.	To reflect the most recent study status.
Section 9.2.4: Regulatory Reporting Requirements for SAEs Appendix 2: Study Governance Considerations	Replacement of Directive 2001/20/EC by Regulation 536/2014.	Update the legal framework of the trial after transition to EU-CTR.
Section 10.1.1: Sample Size Determination of Primary Endpoints	Removed the study-wise final analysis (OS final analyses) and added an interim analysis of PFS B vs A in all lines at the pre-planned analysis at 5-year from first participant randomized.	To fulfill the testing strategy which would allow testing of the secondary endpoints including OS IA in this pre-planned analysis, therefore maintaining the testing strategy.
	Updated the timing of the final analysis (FA) for PFS B vs A in all lines will occur at approximately the 2-year minimum follow-up of all randomized participants.	To mitigate risk of significant delay of readout due to limited accumulation of PFS events beyond the 2-year minimum follow-up for all randomized participants.
Section 10.1.1: Sample Size Determination of Primary Endpoints	Updated to include that PFS B vs C in 1L has been tested at its IA and met the pre-specified statistical criteria.	To confirm the alpha passing based on PFS B vs C in 1L interim analysis result, which is a basis of updated statistical testing parameters.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 10		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.2: Power Calculation of Secondary Endpoints		
Section 10.1.2: Power Calculation of Secondary Endpoints	Updated the projected percentage of the total number of PFS events of arm B vs arm A in 1L that will be observed from 90% to 75% and updated the approximate number of events from 140 to 117.	To update analysis parameters aligning with the updated schedule of PFS analyses.
	Added language in regard to when PFS B vs A in 1L interim analysis will be conducted or skipped.	To align with the updated schedule of PFS analyses.
	Added: "Final analysis of PFS B vs A in 1L will be conducted when approximately 156 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first."	To mitigate risk of significant delay of readout due to potential limited accumulation of PFS events beyond the 2-year minimum follow-up for all randomized participants.
	Updated the timing of the final OS analyses.	To allow extended follow-up for survival data collection mitigate risk of significant delay of readout due to potential significant delay in OS events accumulation.
Section 10.3.11: Interim Analyses	Updated the language for the study-wise IAs planned for primary and secondary endpoints prior to the FA of OS endpoints.	To align with updates in Section 10.1.
	Updated the timing of the final OS analyses.	

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title:

A Phase 3 Randomized Clinical Trial of Nivolumab alone, Nivolumab in Combination with Ipilimumab, or Investigator's Choice Chemotherapy in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

Short Title:

A study of nivolumab, nivolumab plus ipilimumab, or investigator's choice chemotherapy for the treatment of patients with dMMR/MSI-H metastatic colorectal cancer (mCRC).

Study Phase: 3

Rationale:

CA2098HW (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation [CHECKMATE]-8HW) is a Phase 3, randomized, open-label, multi-center 3-arm clinical trial of nivolumab monotherapy, nivolumab plus ipilimumab combination therapy or standard chemotherapy in recurrent or metastatic dMMR/MSI-H CRC across lines of therapy.

Results from non-randomized cohort study CA209142 led to the accelerated approval of nivolumab single agent or in combination with ipilimumab for dMMR/MSI-H metastatic CRC (mCRC) patients who progressed after fluoropyrimidine, oxaliplatin, and irinotecan treatment. Although both nivolumab monotherapy and nivolumab plus ipilimumab combination therapy demonstrated strong clinical activity, indirect comparisons suggested improved clinical benefit of combination therapy vs monotherapy. The CA2098HW is designed to confirm these findings and directly compare the clinical benefit, as measured by progression-free survival (PFS), objective response rate (ORR), and overall survival (OS), achieved by nivolumab in combination with ipilimumab or by nivolumab monotherapy.

It is generally accepted that patients with dMMR/MSI-H metastatic CRC are less responsive to conventional chemotherapy and may have a poorer prognosis than patients with mismatch repair-proficient (pMMR) or MSS mCRC. Studies comparing single agent immunotherapy vs chemotherapy in patients who have not received prior treatment are currently ongoing, however there are no randomized studies evaluating combination of immunotherapies vs chemotherapy. Recently presented data from a randomized phase 3 study comparing pembrolizumab with standard chemotherapy in front-line setting (Keynote-177 study) confirmed superior antitumor activity as reflected by PFS and ORR achieved by anti-PD1 single agent vs chemotherapy in MSI-H mCRC patients. In the CA209142 study, nivolumab plus ipilimumab combination in previously untreated dMMR/MSI-H mCRC patients demonstrated high ORR and durable responses which translated into improvement of PFS and OS. Also, this combination showed favorable safety profile. Promising activity of nivolumab plus ipilimumab combination as 1L treatment in dMMR/MSI-H mCRC patients requires further evaluation, including direct comparison vs current chemotherapy standard of care. This will be evaluated in the CA2098HW study.

The CA2098HW study also includes a pharmacodiagnostic component as part of a post-approval commitment in the US. The study data will be utilized to support the analytical and clinical validation of an immunohistochemistry-based and a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab and/or nivolumab plus ipilimumab combination therapy for patients with tumors that are dMMR/MSI-H.

Study Population:

Male and female participants ≥ 18 years of age, with recurrent or metastatic dMMR/MSI-H CRC not amenable to surgery.

Key Inclusion Criteria:

- Histologically confirmed recurrent or metastatic CRC irrespective of prior treatment history with chemotherapy and/or targeted agents not amenable to surgery. This inclusion criterion is applicable only during Part 1* enrollment of the study.
- Known tumor MSI-H or dMMR status per local standard of practice.
- All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria.
- Adequate tumor tissue available. Tumor tissue specimens, either a FFPE tissue block (preferred) or unstained tumor tissue sections (minimum of 30 positively charged slides) from primary or metastatic site, must be submitted to the central laboratory. Central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Tumor tissue specimen must meet either of the criteria below:
  - Obtained within 3 months of enrollment with no intervening systemic anti-cancer treatment between time of acquisition and randomization AND this must be the same tissue sample as was used for local MMR/MSI testing;

    OR
  - If above is not available, archival tissue can be accepted if the same tissue was used for MMR/MSI testing.

  Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone samples are also unacceptable for submission.
- ECOG Performance Status ≤1
- Histologically confirmed recurrent or metastatic CRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery. Participants treated with adjuvant chemotherapy are eligible if disease progression occurred later than 6 months (≥ 6 months) after completion of chemotherapy. This inclusion criterion is applicable during Part 2* enrollment of the study.

*Refer to Overall Design section for details

Key exclusion criteria:

- 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.

- Participants with an active, known or suspected autoimmune disease.
- History of interstitial lung disease or pneumonitis.
- Known history of positive test for HIV or known AIDS.
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
- Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency. Systematic screening for DPD deficiency has to be performed at sites where mandated locally.

Additional exclusion criteria for participants who have not received prior systemic therapy or who have received one prior line of systemic therapy.

- Prior major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization. Any wound-related AE(s) must have resolved prior to randomization.
- Clinically significant cardiovascular disease, including but not limited to congenital long QT syndrome. Pre-existing hypertension should be adequately controlled.
- Clinically significant bleeding diathesis or coagulopathy.
- Myocardial infarction, arterial thrombosis or cerebrovascular accident within 6 months prior to enrollment.
- History of gastrointestinal perforation or abscess within 6 month prior to enrollment.
- Persistence of toxicities related to first-line chemotherapy Grade > 1 (CTCAE v5.0) (except alopecia, fatigue or peripheral sensory neuropathy which can be Grade 2)

Objectives and Endpoints:

The study includes two target populations and objectives are set up according to the populations. The randomized participants regardless of prior lines of therapy will refer to 'All lines' and the randomized participants who have not received prior therapy for metastatic disease will refer to '1L'.

Primary Objective	**Endpoint**
• **All lines**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B vs A)
• **1L**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR (arm B vs C)

Secondary Objective	**Endpoint**
• **All lines**	
To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	ORR by BICR (arm B vs A)
To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	OS (arm B vs A)
To estimate the Investigator-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by Investigator assessment (arm A and B)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who were randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR among all randomized participants (arm A and B)
• **1L**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B vs A)
To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	ORR by BICR (arm B vs C)
To compare the BICR -assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	ORR by BICR (arm B vs A)

Secondary Objective	Endpoint
To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	OS (arm B vs A)
To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm	PFS by BICR (arm A and C)
To estimate the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	OS (arm B and C)
To estimate the BICR assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm	ORR by BICR (arm A and C)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR among all randomized participants who have not received prior treatment (arm B and C)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR among all randomized participants who have not received prior treatment (arm A and B)
• **CDx (All lines and 1L)**	
To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR (arm B and C)
To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B and A)
• **Crossover Cohort**	
To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort	PFS by BICR
To estimate the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort	ORR by BICR

Overall Design:

CA2098HW is a Phase 3, randomized, 3-arm open-label study of nivolumab monotherapy (arm A), nivolumab plus ipilimumab combination therapy (arm B) or investigator's choice chemotherapy (arm C) for treatment of participants with recurrent or metastatic dMMR/MSI-H CRC. In protocol revision 04, the study expanded to include additional participants in 1L setting. Therefore, the study enrollment includes 2 sequential parts. Part 1 enrollment is open to participants across all lines of therapy, and Part 2 enrollment is open only to participants who have

not received prior therapy for metastatic disease (1L). Part 2 enrollment starts immediately after completion of part 1 enrollment.

After confirmation of eligibility criteria participants will be randomized to arms A, B or C in a 2:2:1 ratio. Randomization to arm C will be restricted to participants who have received no more than 1 prior line of systemic therapy (0 or 1 line). Part 1 enrollment continues to allow randomization of approximately 442 participants across lines of therapy with centrally confirmed dMMR/MSI-H mCRC as per protocol revision 03.

Approximately 230 additional participants who have not received prior therapy for metastatic disease (1L) with centrally confirmed dMMR/MSI-H mCRC will be randomized during part 2 enrollment.

A continuous evaluation of the discordance rate between local and central testing during the study conduct suggests that approximately 15% of the samples have discordant dMMR/MSI-H results. The observed discordance rate is higher than the initially assumed rate of 10% used for sample size calculation for randomization per local testing. Additionally, poor tissue quality led to the absence of valid central test results in some instances; ie, no confirmation of dMMR/MSI-H status by either central test. Therefore, while the projected number of randomized participants per central testing have not changed, the number of participants per local testing is revised to reflect higher than initially assumed discordance rate.

Part 1 enrollment was completed as of Revised Protocol 06. Part 2 randomization was completed in Apr-2023.

Stratification factors

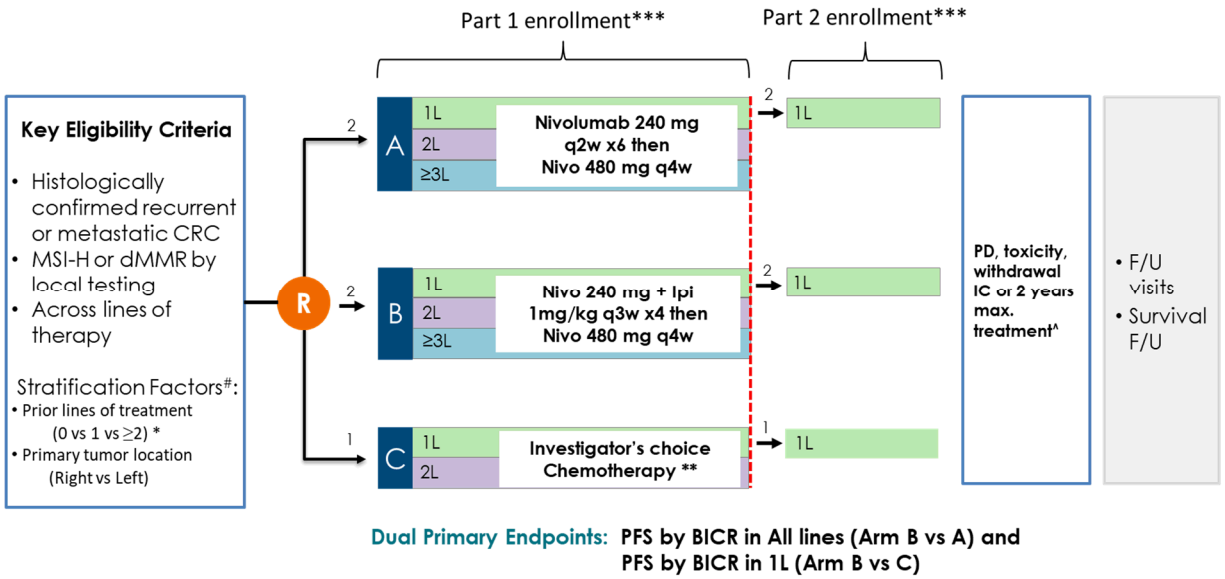
CA2098HW study participants will be stratified by tumor location (right vs left) and by the number of prior treatments for metastatic disease (none, one, two or more). Stratification by tumor sidedness will continue during Part 2 enrollment, however stratification by line of therapy will not be applicable since enrollment will be open only for participants who have not received prior therapy. Study specific definition of tumor sidedness and line of therapy (number of prior systemic treatments for metastatic disease) are provided in the Appendices 12 and 10, respectively.

Crossover Cohort

Participants assigned to arm C who experience documented progression of disease (PD) per RECIST 1.1 by Blinded Independent Central Review (BICR) will have an option to crossover to nivolumab plus ipilimumab therapy (Crossover Cohort) provided that they complete at least Follow Up Visit 1 within the Follow Up phase and meet all other crossover criteria outlined in the protocol. Crossover Cohort participants will receive treatment until progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration. After study treatment discontinuation, they will also enter the Follow Up phase (second treatment Follow Up) and will follow the assessment schedules. The Crossover Cohort starts when participants begins nivolumab plus ipilimumab combination therapy.

The study design schematic is presented in Figure 1.

Figure 1 Study Design Schematic



Abbreviations: BICR, Blinded Independent Central Review; CRC, colorectal cancer; IC, informed consent, MSI-H, microsatellite instability high; dMMR, deficient mismatch repair; PD, progressive disease; PFS, progression free survival

1L, 2L, ≥3L – subgroups of participants within each study arm for whom study treatment is a 1st line (0 prior lines of systemic therapy), 2nd line (1 prior line of systemic therapy) or 3rd line and beyond (2 or more prior lines of systemic therapy), respectively.

Line of therapy is not a stratification factor during Part 2 enrollment.

* Participants with ≥2 prior lines are randomized only to arm A or B during Part 1; only participants with 0 prior lines are randomized during Part 2 enrollment.

** Optional Crossover for arm C with Nivo + Ipi q6w dosing

*** Part 1 enrollment continues to allow randomization of approximately 560 participants across lines of therapy with locally confirmed dMMR/MSI-H mCRC. Part 2 enrollment continues to allow randomization of approximately 271 additional participants with locally confirmed dMMR/MSI-H status who have not received prior therapy for metastatic disease (1L). Part 2 randomization was completed in Apr-2023.

^ max treatment duration is not applicable for arm C participants

Number of Participants:

It is expected that approximately 831 participants with dMMR/MSI-H mCRC determined by local testing will be randomized to study, including approximately 560 and 271 during part 1 and part 2 enrollment, respectively. These correspond to randomization of approximately 442 participants across lines of therapy and 230 participants who have not received prior treatment with centrally confirmed dMMR/MSI-H status during part 1 and part 2 enrollment, respectively. These estimations are based on the number of participants with centrally confirmed dMMR/MSI-H status required for evaluation of each primary endpoint and on assumption of discordance rate between local and central testing of 15%.

Treatment Arms and Duration:

Arm A (Nivolumab monotherapy): Nivolumab 240 mg administered every 2 weeks (Q2W) for up to 6 doses (2 cycles), followed by nivolumab 480 mg administered every 4 weeks (Q4W) until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.[a]

Arm B (Nivolumab plus ipilimumab): Nivolumab 240 mg plus ipilimumab 1 mg/kg both administered every 3 weeks (Q3W) for up to 4 doses (2 cycles), followed by nivolumab 480 mg administered every 4 weeks (Q4W) until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.[a]

Arm C (Investigator's Choice Chemotherapy): One of 6 Investigator's choice chemotherapy regimens (mFOLFOX6; mFOLFOX6 + bevacizumab; mFOLFOX6 + cetuximab; FOLFIRI; FOLFIRI + bevacizumab; FOLFIRI + cetuximab) administered every 2 weeks (Q2W) until disease progression, unacceptable toxicity, withdrawal of consent.

In addition, arm C participants that experience BICR-documented progression on or after treatment, will have the option to enroll in the Crossover Cohort to receive nivolumab in combination with ipilimumab.

Crossover Cohort (Nivolumab plus ipilimumab): Nivolumab 240 mg administered every 2 weeks (Q2W), for up to 6 doses (2 cycles), followed by nivolumab 480 mg administered every 4 weeks (Q4W) thereafter. Ipilimumab will be administered at a dose of 1 mg/kg every 6 weeks continuously (Q6W). Both nivolumab and ipilimumab will be administered until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.[b]

[a]**maximum treatment duration** for arm A or arm B will be 2 years from the first dose of study treatment EXCEPT in participants with late response (during second year of treatment). In participants with late response study treatment will continue for up to an additional 12 months after onset of response, in absence of disease progression, unacceptable toxicity, withdrawal of consent. Above defined maximum treatment duration includes treatment beyond progression.

[b]Participants enrolled to Crossover Cohort may have **maximum treatment duration,** including treatment beyond progression, of 2 years from the first dose in Crossover Cohort.

Study treatment:

Study Drug for CA2098HW		
Medication	**Potency**	**IP/Non-IP**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP

Study Drug for CA2098HW		
Medication	**Potency**	**IP/Non-IP**
Ipilimumab Solution for Injection	200 mg (5 mg/mL) and 50 mg (5 mg/mL)	IP
Oxaliplatin[a,b]	various strengths	IP
Leucovorin (folinic acid)[a,b]	various strengths	IP
Fluorouracil[a,b]	various strengths	IP
Irinotecan[a,b]	various strengths	IP
Bevacizumab[a,b]	various strengths	IP
Cetuximab[a,b]	various strengths	IP

[a] These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. In these cases, products may be in a different pack size/potency/pharmaceutical form than listed in the table. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics.

[b] Potency, packaging, and storage conditions may vary for China. Storage conditions will be indicated on the label.

Data Monitoring Committee: Yes

Sample Size Determination:

During part 1 enrollment, participants who have received no more than 1 prior line of systemic therapy (0 or 1) will be randomized to nivolumab monotherapy arm (arm A), nivolumab plus ipilimumab combination therapy arm (arm B) or investigator's choice of chemotherapy arm (arm C) at a 2:2:1 ratio. Participants who have received 2 or more prior lines of systemic therapy will be randomized to arm A or to arm B at a 1:1 ratio. Among all randomized participants it is expected that the proportion of those who have had 0 prior line of systemic therapy (1L) will be approximately 35%, those who had 1 prior line of systemic therapy (2L) will be approximately 35%, and those who have had a least 2 lines of systemic therapy (3L+) will be approximately 30%. Part 2 enrollment was added in protocol revision 04, in order to provide appropriate power for PFS comparison among 1L participants between arms B vs C and arms B vs A. Only participants who have no prior line of systemic therapy (ie, participants for whom study treatment is a 1L therapy) will be randomized at 2:2:1 ratio to arms A, B and C during Part 2.

Comparisons of an efficacy endpoint (eg, PFS, ORR, or OS) between given two arms will be based on concurrently randomized participants to the corresponding two arms, except when otherwise specified.

Participants will be enrolled based on local evaluation of their dMMR/MSI-H status but the primary efficacy population will consist of participants with centrally confirmed dMMR/MSI-H mCRC by either central test (IHC or PCR-based). It is expected that approximately 15% of the participants may not have their local dMMR/MSI-H mCRC confirmed centrally. The sample size calculation is based on randomized participants with dMMR/MSI-H status confirmed by central tests. Unless otherwise specified, "participants" of Study CA2098HW mentioned in this section refer to "randomized participants with dMMR/MSI-H status confirmed by central tests"; clinical outcomes (e.g., "event," "response," etc) of Study CA2098HW mentioned in this section refer to those observed among randomized participants with dMMR/MSI-H status confirmed by central tests.

The sample size of this study will be driven by the comparison of the two primary endpoints and the secondary endpoint of PFS comparison between 1L participants randomized to arm B and arm A:

1. PFS comparison between participants randomized to arm B and arm A during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs A in all lines'
2. PFS comparison between participants who have not received prior line of systemic therapy and randomized to arm B and arm C during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs C in 1L'.
3. PFS comparison between participants who have not received prior line of systemic therapy and randomized to arm B and arm A during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs A in 1L'.

In order to control the overall type I error at 5%, for the purpose of sample size calculation, the alpha is initially split between the two primary endpoints, with 0.6% for PFS B vs A in all lines and 4.4% for PFS B vs C in 1L. The secondary endpoint of PFS B vs A in 1L will be tested hierarchically. The testing procedure for the other secondary endpoints is provided in the protocol.

PFS comparison in all lines between arm B vs arm A

Prior to the revised protocol 04, based on the observed PFS curve and rates at different time points in the nivolumab monotherapy cohorts of CA209142 (data on file, results from August 2018 database lock), the PFS distribution for nivolumab monotherapy (arm A) was assumed to be piecewise exponential.

Since both arm A and arm B are immunotherapies, no delayed separation of PFS KM curves will be expected.

Initially a constant hazard ratio (HR) of 0.65 for arm B compared with arm A is assumed which therefore translates to piecewise exponential distribution of PFS in arm B. Under these assumptions, the median estimates for PFS is 6 months and 27 months for monotherapy and combination therapy arms, respectively.

Approximately 354 PFS events will provide about 90% power to detect a HR of 0.65 with an overall type 1 error of 0.006 (two-sided). Under the assumption of a staggered enrollment, it is

required to randomize approximately 564 participants to both arm A and B during Part 1 and Part 2 enrollment.

This initial design accounts for one PFS interim look when approximately 80% of the total number of events are observed (approximately 283 events). It is projected that Part 1 enrollment will take approximately 16 months and Part 2 enrollment will take approximately 14 months. The timing of final analysis is projected to be 49 months from the date of first participant being randomized during Part 1 enrollment.

At the time of protocol revision 04 development, the updated data from CA209142 and published data from Keynote-177 suggested updated assumptions on PFS rates of arm A and HR of arm B vs arm A in all lines. Based on the updated assumptions, approximately 319 events will provide about 90% power to detect a HR of 0.635 with an overall type 1 error of 0.006 (two-sided). The final analysis of the primary endpoint of PFS B vs A in all lines will be conducted when at least 319 PFS events are observed, which is projected to be approximately 50 months after the first participant is randomized during Part 1 enrollment. An interim analysis will be conducted when approximately 85% of the total number of events are observed (approximately 271 events) and after the last participant is randomized during Part 2 enrollment.

If PFS B vs C in 1L meets the pre-specified statistical criteria at the interim or final analysis and 0.024 alpha is passed to PFS B vs A in all lines, 319 PFS events will provide approximately 96.8% power with two-sided alpha of 0.03 for HR of 0.635.

Due to the delay of PFS events, the pre-planned, study-wise final analysis (OS final analyses, planned to occur around 5 years from the first participant's randomization, which is around Aug-2024) is no longer feasible because it will deviate from the testing strategy. In order to maintain the testing strategy in the pre-planned analysis around Aug-2024, the study-wise final analysis for OS at the 5-year mark is removed and an interim analysis of PFS B vs A in all lines is added at this time. It is projected that the PFS events for Arm B vs A in all lines will reach approximately 240 events (~75% of the total number of events) around Aug-2024. If PFS B vs A in all lines meets its pre-specified statistical significance in this IA, the secondary endpoints including OS (IA) are allowed to be tested following the testing strategy. The originally planned PFS IA B vs A in all lines at approximately 271 events will be the second IA after the one around Aug-2024. The target number of events for the PFS FA B vs A in all lines (approximately 319 events) remain unchanged. The final analysis of PFS B vs A in all lines will be conducted when approximately 319 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first.

Therefore, PFS B vs A in all lines will have 2 IAs (1 at approximately 240 events with a data cut-off in around Aug-2024 [newly added] and 1 at approximately 271 events [previously planned]) and a FA (previously planned, but with updated timing: when approximately 319 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first). The 2nd IA will be skipped if the projected time of the 2nd PFS IA B vs A in all lines is too close to the proposed PFS FA time (eg, less than 6 months apart), or it is projected to be after the proposed PFS FA time.

The significance level for the PFS IA(s) will be determined based on the observed information fraction of the planned total number of 319 events. If the second IA is skipped, no alpha will be spent for the second IA and the remaining alpha level after the first IA will be used at the FA. The significance level for the PFS FA will be calculated according to the actual alpha(s) spent at IA(s). If less than 319 events are observed, the significance level will be based on the planned 319 events without further adjustment for the actual total number of PFS events.

PFS in 1L for comparison between arm B vs arm C

The sample size for the PFS B vs C in 1L is determined with the following additional assumptions:

- The distribution of PFS in arm A in 1L is assumed based on observed data in Keynote-177. The PFS rates in arm B in 1L are assumed on the basis of a constant HR of 0.6 vs arm A in 1L.
- The distribution of PFS in arm C in 1L follows an exponential distribution with median PFS of 9 months.

Based on simulations, approximately 125 PFS events will provide about 99% power to detect an average HR of 0.55 with an overall type 1 error of 0.044 (two-sided). Under the assumption of a staggered enrollment, it is required to randomize approximately 230 1L participants to arms B and C during Part 1 and Part 2 enrollment at 2:1 ratio.

This design accounts for one PFS interim look when 85% of the total number of events are observed (approximately 106 events) and after the last participant is randomized during Part 2 enrollment. The final analysis is projected to be approximately 47 months, from the date of first participant being randomized during Part 1 enrollment.

To ensure the sample size is sufficient for both of the primary endpoints as discussed above, Part 1 randomization will be closed when approximately 442 participants are randomized with central lab confirmed dMMR/MSI-H. This translates to an approximate number of participants in arm A (N=190), B (N=190) and C (N=62 as arm C will only randomize participants who received 0 or 1 prior lines of therapy). During Part 2 enrollment approximately 230 1L participants with central lab confirmed dMMR/MSI-H will be randomized. This translates to an approximate number of participants in arm A (N=92), B (N=92) and C (N=46).

PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. Therefore, PFS B vs C in 1L is concluded and will not be tested again in a final analysis.

Power calculation for PFS in 1L for comparison between arms B vs A

The PFS comparison between arm B vs arm A for 1L participants is the first secondary endpoint. Using the sample size as determined for the primary endpoints, the power calculation for PFS B vs A in 1L is calculated under the following assumptions:

- The PFS KM curve in arm A 1L follows the piece-wise exponential distribution
- A constant HR of 0.6 is assumed for PFS in 1L arm B vs arm A

- The concurrent randomization ratio of arm B vs arm A is 1:1. Based on the sample size determined by the primary endpoints, it is estimated that a total of 308 1L participants will be concurrently randomized to arms A and B
- One interim analysis of PFS of arm B vs arm A in 1L is planned. PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. If PFS B vs A in all lines meets its pre-specified statistical criteria at its first interim analysis with the data cut-off in around Aug-2024, interim analysis of PFS B vs A in 1L will be conducted at the same time. It is projected that approximately 75% of the total number of PFS events of arm B vs arm A in 1L will be observed (approximately 117 events) in around Aug-2024. If PFS B vs A in all lines does not meet the pre-specified statistical criteria at its first interim analysis, PFS B vs A in 1L interim analysis will be skipped and the endpoint will be tested at its final analysis. Details on the testing procedure is described in Section 10.3.10.
- Under the above assumptions, a total of 156 PFS events will provide approximately 87% power with two-sided alpha of 0.044 to demonstrate statistical significance of arm B vs arm A in 1L. If PFS B vs A in all lines does not meet the pre-specified statistical criteria in the final analysis and PFS B vs A in 1L is tested with alpha of 0.02 passed only from PFS B vs C in 1L, 156 PFS events will provide approximately 79.5% power. Final analysis of PFS B vs A in 1L will be conducted when approximately 156 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first.

Primary Endpoints and Statistical Analyses

The primary efficacy population will be the "Confirmed dMMR/MSI-H" participants. Appropriate analyses will be performed for "Confirmed dMMR/MSI-H by IHC" and "Confirmed dMMR/MSI-H by PCR" to demonstrate comparable efficacy based on dMMR/MSI-H by one of the central tests. These analyses will support the clinical utility of the IVD for each of the central test. The SAP will document further details. The endpoint defined below will apply to both "All participants" and "1L participants," unless otherwise specified.

Endpoint	**Statistical Analysis Methods**
Primary	
BICR-assessed Progression-free survival (PFS) is defined as the time from the randomization date to the date of first objectively documented disease progression per RECIST 1.1 (ie, radiologic) or death due to any cause, whichever occurs first. • Participants who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death.	The distribution of PFS will be compared via a two-sided, log-rank test stratified by randomization stratification factors of line of therapy (not applicable to PFS in 1L) and tumor sidedness recorded in IRT at the allocated significance level at IA and FA. 1L endpoints, stratified analyses will exclude 'lines of therapy' as a stratification factor.

Endpoint	Statistical Analysis Methods
• Participants who did not progress or die will be censored on the date of their last tumor assessment • Participants who did not have any on study tumor assessments and did not die will be censored on the randomization date. • Participants who started any subsequent anti-cancer therapy without a prior reported progression or prior to death will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. • Further explanation for various censoring scenarios for PFS will be specified in SAP.	The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha) % confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate, stratified by line of therapy and tumor sidedness as recorded in IRT. PFS curves will be estimated using Kaplan-Meier (KM) product-limit methodology. Median PFS with two-sided 95% confidence interval (CI) using the Brookmeyer and Crowley method (with log-log transformation) will be computed. In addition, PFS rates at a specific time point (eg, 6, 12, 24 months) with two-sided 95% CI using the log-log transformation will be computed.

Interim Analyses

The DMC will be utilized to provide an independent evaluation of the study interim data. An independent statistical group will be utilized to conduct unblinded monitoring of pooled events of the two corresponding arms of each comparison in order to track the number of events by each comparison.

Study-wise, there are two interim analyses (IA) planned for primary and secondary endpoints prior to the final analysis of OS endpoints.

- The first interim analysis of the study is planned for the interim analysis for both the primary endpoints of PFS. Considering the variability of the enrollment assumptions from the actual enrollment rate and differences of the shape of PFS curves in arms A, B, and C, this study plans to have the interim analysis of PFS for the 2 primary endpoints at the same time when the latest of the targeted number of events of each endpoint is observed and after the last participant is randomized during Part 2 enrollment. In other words, the first interim analysis of the study was planned to be triggered when at least 85% of the total number of events were observed for both PFS primary endpoints and after the last participant randomized during Part 2 enrollment. Separate database locks for IA PFS B vs C in 1L and IA PFS B vs A in all lines may be conducted if the locks are expected to occur at least 3 months apart from each other. As of Protocol Amendment 10, PFS B vs C in 1L has been

tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. Interim analysis of PFS B vs A in all lines will be conducted in a separate DBL with a data cut-off in around Aug-2024 ("PFS B vs A all lines IA1 DBL"). If PFS B vs A in all lines does not meet the pre-specified statistical criteria in this first interim look, a second interim look ("PFS B vs A all lines IA2 DBL") may be conducted if the projected time between the second interim look and final look is more than 6 months. The interim analysis of the secondary endpoint PFS B vs A in 1L will be conducted when PFS B vs A in all lines meets the pre-specified statistical criteria at its interim analysis. The stopping boundaries at the interim analysis for each of the PFS endpoints will be derived based on the exact number of events observed in the locked database using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. For any PFS endpoint, if the timing of interim analysis based on this trigger is too close to the projected time of its final analysis (eg, within 6 months), the interim analysis of this specific PFS endpoint may be skipped and the endpoint will be tested at the final analysis.

- Since PFS B vs C in 1L has been concluded, the second interim analysis of the study will be the final analysis of PFS B vs A in all lines and PFS B vs A in 1L, which will be conducted when the required number of total events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first.
- The final analysis of this study will include the final OS analysis for arm B vs arm A in all lines, Arm B vs Arm C in 1L, and Arm B vs Arm A in 1L, which will be conducted 3 years after the last participant in Part 2 enrollment was randomized.
- As described above, these interim and final analyses may be triggered by more than one endpoint and therefore all the events observed in the two arms for the corresponding comparisons will be used for the analyses. For a given endpoint, the stopping boundaries (alpha allocation) at the interim analysis will be derived based on the exact number of events observed in the locked database (vs target number of events at final analysis) using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. In the scenario that the final analysis of an endpoint is event-driven and the locked database has more events than planned, the final allocation of alpha will be adjusted based on actual number of events observed at the final analysis.

Once one of the primary endpoints of PFS meets the pre-specified statistical criteria at the interim or final analyses, the secondary and exploratory endpoints in the same set of participants will be analyzed. Secondary endpoints (to be tested under the testing procedure) which have not met the pre-specified statistical significance level may not be reported in an aggregated fashion and be analyzed at the final analysis.

In addition, an ad hoc interim analysis of ORR estimation in arm A, B and arm C for 1L participants may be conducted to support potential 1L regulatory submission requirements. No statistical comparison will be made among arms. Should such an interim analysis occur, the SAP will specify the details, including the timing, and number of participants to be used, prior to the database lock.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2098HW)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. Register in IRT to obtain participant number. If participant meets criteria for re-enrollment, (see Section 6.5.1), the participant must be re-consented and assigned a new participant number via IRT.
Inclusion/Exclusion Criteria	X	Assessed during screening period (and re-enrollment, if applicable). Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study. Includes: concomitant medications, smoking history (including electronic cigarettes) and alcohol history.
Review previous anti-cancer treatment	X	As applicable. Please refer to Appendix 10 for study specific definition of the line of therapy (number of prior systemic treatments for metastatic disease) that is required for proper stratification and randomization of participants.
Tumor Tissue Sample	X	Either a FFPE tissue block (preferred) or unstained tumor tissue sections (minimum of 30 positively charged slides), from primary or metastatic site, meeting either of the following criteria must be submitted to the central laboratory: 1) Obtained within 3 months of enrollment with no intervening systemic anti-cancer treatment between time of acquisition and randomization AND this must be the same tissue sample as was used for local MMR/MSI testing; • OR 2) If above is not available, archival tissue can be accepted if the same tissue was used for MMR/MSI testing. Central lab must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Tumor tissue should be excisional, incisional or core needle biopsies or surgical specimens. Fine needle biopsies are not acceptable. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone samples are also not acceptable.

Table 2-1: Screening Procedural Outline (CA2098HW)

Procedure	Screening Visit[a]	Notes
MMR/Microsatellite Status per local testing	X	Sites must submit and document prior MMR/MSI testing and results. Confirm availability of pathology report for MMR or microsatellite-testing results. Report should also contain specific results of markers tested by IHC or PCR-based method. Refer to Inclusion criteria (see Section 6.1) and Appendix 8 for details.
Baseline Tumor Assessment	X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all known sites of disease should be performed within 28 days prior to randomization. See Section 9.1.1.1.
Brain Imaging	X	MRI of the brain with and without contrast is required if participant is symptomatic or has a history of brain metastasis, and has not had brain imaging within 30 days of anticipated randomization. CT of the Brain (with and without contrast) can be performed if MRI is contraindicated. See Section 9.1.1.1.
Other Imaging (eg, Bone Scan)	X	As clinically indicated per local standards. See Section 9.1.1.
Safety Assessments		
Physical Examination, Measurements, Vital Signs and ECOG Performance Status	X	Must be collected within 14 days prior to randomization. Height, weight, BP, HR, temperature and Performance Status (see Appendix 6) must be obtained.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Concomitant Medication Use and Vaccination	X	Within 14 days prior to randomization. Record vaccine use within 30 days prior to randomization.
SAE Assessment	X	SAEs from time of consent. See Section 9.2, and Appendix 3 All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
ECG	X	Within 14 days prior to randomization. 12-lead ECG is required.
Laboratory Tests		
Laboratory Tests (CBC w/differential, Chemistry, Endocrine, Viral)	X	CBC with differential, chemistry, urinalysis, and endocrine testing must be performed within 14 days prior to randomization. Viral testing to be performed within 28 days prior to randomization. For HIV: testing at sites where locally mandated; see Appendix 9 for country-specific requirements.

Table 2-1: Screening Procedural Outline (CA2098HW)

Procedure	Screening Visit[a]	Notes
		Where locally required testing for Dihydropyrimidine dehydrogenase (DPD) deficiency should be done at any time during screening. If testing for DPD-deficiency was done prior to study entry and the medical documentation is available there is no need to repeat testing. See Appendix 9 for country-specific requirements. For full list of assessments to be performed, see Section 9.4.4.
History of determination of tumor gene status for RAS and BRAF	X	RAS mutation status (KRAS and NRAS), BRAF mutation status, and history of Lynch syndrome (genetic testing results) if available.
CEA and CA19-9 Assessment	X	CEA and CA19-9 tumor markers to be assessed at any time during screening. If CEA is within normal limits and CA19-9 is elevated, this patient will be followed with both the CEA and CA19-9 tumor markers. However, if the CA19-9 is within normal limits, this patient will be followed with CEA tumor marker only.
Urinalysis[b]	X	At screening and must be performed within 14 days prior to randomization. See Section 9.4.4
Stool Samples for Microbiome Analysis	X	Stool sample to be collected within 7 days prior to first dose.
SARS-CoV-2 Serology	X	Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3])
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and 24 hours prior to first dose of study treatment. For females under the age of 55, FSH > 40 mIU/mL is required to confirm menopause. See Appendix 4.

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

[b] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required. If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis, results from a 24-hour urine collection or urine protein to creatinine ratio (UPCR) are required to determine eligibility (refer to exclusion criteria).

Abbreviations: BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HCG, human chorionic gonadotropin; HR, heart rate; IgG, immunoglobulin G; IHC, immunohistochemistry; IRT, Interactive Response system; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI,

microsatellite instability; PCR, polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child bearing potential.

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Safety Assessments						
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	Weight, BP, HR, temperature and Performance Status (see Appendix 6). Obtain prior to each dose.
Review of Concomitant Medications and Vaccination	Continuously				X	Record at each visit.
AE Assessment (including SAE Assessment)	Continuously				X	Record at each visit. All AEs (SAEs or non-serious AEs), must be collected continuously during the treatment period.
Clinical Laboratory Tests (CBC w/differential, Chemistry)	X	X	X	X		On site/ local laboratory testing should be done within 72 hours prior to each dose. Screening labs are acceptable if performed within the previous 72 hours and results are available. For full list of assessments to be performed, see Section 9.4.4
Endocrine function testing	X	X (see note)				Thyroid function testing should be done every 6 weeks for the first 24 weeks, and then every 8 weeks until completion of study treatment. **C4D15** testing falls where there is no corresponding dosing and can be performed at the preceding dosing visit (C4D1). If clinically indicated

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
						additional tests (ACTH, cortisol) to be performed per local requirements. See Section 9.4.4
CEA and CA19-9 Assessment	X	X (see note)			X	CEA alone or CEA and CA19-9 will be assessed prior to each restaging (every 6 weeks (± 7 days) for the first 24 weeks, and every 8 weeks (± 7 days) thereafter). Sample collection can be obtained at the corresponding dosing visit. **C4D15** testing falls where there is no corresponding dosing and can be performed at the preceding dosing visit (C4D1).
Pregnancy Test (WOCBP only)	X	C1D29	C2D15	X		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Health Outcomes						
EORTC QLQ-C30 Questionnaire	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
						delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs
EORTC QLQ-CR29 Questionnaire	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
EQ-5D-3L Questionnaire	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1 and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs
Efficacy Assessments						
Tumor assessments[d]	See note					**During first 96 weeks from randomization (Year 1 and 2)** Tumor assessment should occur every 6 weeks (± 7 days) from randomization for the first 24 weeks, and every 8 weeks (± 7 days) thereafter, until BICR confirmed progression, and treatment discontinuation (including treatment beyond progression), whichever occurs later. This schedule should be followed even if treatment delay occurs. See Section 9.1.1 for further details.

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
						During week 97 - 144 from randomization (Year 3) Tumor assessment should occur every 16 weeks (± 7 days) until BICR confirmed progression. See Section 9.1.1 for further details. **Beyond week 144 from randomization (Year 4 and beyond)** Tumor assessment should occur every 24 weeks (± 14 days) until BICR confirmed progression. See Section 9.1.1 for further details.
Brain Imaging	See note					Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). See Section 9.1.1 for further details.
Other Imaging (eg, Bone Scan)	See note					As clinically indicated per local standards. See Section 9.1.1 for further details.

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Pharmacokinetic /Immunogenicity Assessments						
PK and Immunogenicity samples	X	See note				See Table 9.5-1 for time points of collection.
Biomarker Assessments						
Exploratory Plasma Biomarkers, Whole Blood DNA, MDSC, PBMC, Serum	X	X (See note)			X (see note)	See Table 9.8-1 for time points of collection.
SARS-CoV-2 Serology[e]		X (See note)				Serum collected approximately every 6 cycles during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3]).
Stool samples for microbiome analysis	C2D1				X (see note)	See Table 9.8-1 for time points of collection. Samples may collected within 3 days prior to dosing.

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Collection of tumor tissue for biomarker research on-treatment and upon disease progression	C1D22-28 (1 week after 2nd dosing and before the 3rd dosing)				X (see note)	Tumor tissue submission while on-treatment (1 week after 2nd dosing and before the 3rd dosing, i.e. between Day 22-28 of Cycle 1) and upon progression (PD + 14 days) is optional but strongly recommended to understand the response/resistance to nivolumab treatment. See Table 9.8-1 for time points of collection. If biopsy or surgical resection is performed per protocol while on treatment or at progression, a tumor sample (block [preferred] or slides) should be submitted to central laboratory. If biopsies/surgical resection are done at any other time on treatment, tissue samples should be submitted as well.
Clinical Drug Supplies						
Randomization	X					
IRT Drug Vial Assignment						Participant must receive the first dose of study medication within 3 days after randomization.

Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Nivolumab 240 mg flat dose IV	X	X	X			
Nivolumab 480 mg flat dose IV				X		

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

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

[c] Treatment to progression, unacceptable toxicity, withdrawal of consent, or maximum treatment duration as specified in Section 7.1.1

[d] Any additional imaging, including unscheduled timepoints, that may demonstrate tumor response/progression should be submitted to BICR.

[e] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CR29 Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-3L Questionnaire, EuroQol Five-Dimensional Questionnaire, Three-Level Questionnaire; HR, heart rate; IgG, immunoglobulin G; IRT, Interactive Response system; MDSC, myeloid-derived suppressor cell, MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; PD, progressive disease; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child bearing potential.

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Safety Assessments						
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	Weight, BP, HR, temperature and Performance Status (see Appendix 6). Obtain prior to each dose.
Review of Concomitant Medications and Vaccination	Continuously				X	Record at each visit.
Adverse Events Assessment (including SAE Assessment)	Continuously				X	Record at each visit. All AEs (SAEs or non-serious AEs) must be collected continuously during the treatment period.
Clinical Laboratory Tests (CBC w/differential, Chemistry)	X	X	X	X		On site/ local laboratory testing should be done within 72 hours prior to each dose. Screening labs are acceptable if performed within the previous 72 hours and results are available. For full list of assessments to be performed, see Section 9.4.4
Endocrine function testing	X	X (see note)				Thyroid function testing should be done every 6 weeks for the first 24 weeks, and then every 8 weeks until completion of study treatment. **C4D15** testing falls where there is no corresponding dosing and can be performed at the preceding dosing visit (C4D1). If clinically indicated additional tests (ACTH, cortisol) to be performed per local requirements. See Section 9.4.4

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
CEA and CA19-9 Assessment	X	X (see note)			X	CEA alone or CEA and CA19-9 will be assessed prior to each restaging (every 6 weeks (± 7 days) for the first 24 weeks, and every 8 weeks (± 7 days) thereafter). Sample collection can be obtained at the corresponding dosing visit. **C4D15** testing falls where there is no corresponding dosing and can be performed at the preceding dosing visit (C4D1).
Pregnancy Test (WOCBP only)	X	X	X	X		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Health Outcomes						
EORTC QLQ-C30 Questionnaire	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
EORTC QLQ-CR29	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
EQ-5D-3L Questionnaire	X		C2D1	See note		Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Efficacy Assessments						
Tumor assessments[d]	See note					**During first 96 weeks from randomization (Year 1 and 2)** Tumor assessment should occur every 6 weeks (± 7 days) from randomization for the first 24 weeks, and every 8 weeks (± 7 days) thereafter, until BICR confirmed progression, and treatment discontinuation (including treatment beyond progression), whichever occurs later. This schedule should be followed even if treatment delay occurs. See Section 9.1.1 for further details. **During week 97 - 144 from randomization (Year 3)** Tumor assessment should occur every 16 weeks (± 7 days) until BICR confirmed progression. See Section 9.1.1 for further details. **Beyond week 144 from randomization (Year 4 and beyond)** Tumor assessment should occur every 24 weeks (± 14 days) until BICR confirmed progression. See Section 9.1.1 for further details.

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Brain Imaging	See note					Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). See Section 9.1.1 for further details.
Other Imaging (eg, Bone Scan)	See note					As clinically indicated per local standards. See Section 9.1.1 for further details.
Pharmacokinetic /Immunogenicity Assessments						
PK and Immunogenicity samples	X	See note				See Table 9.5-2 for time points of collection.
Biomarker Assessments						
Exploratory Plasma Biomarkers, Whole Blood DNA, MDSC, PBMC, Serum	X	See note			X (see note)	See Table 9.8-2 for time points of collection.
SARS-CoV-2 Serology[e]		X (See note)				Serum collected approximately every 6 cycles during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3]).
Stool samples for microbiome analysis	C2D1				X (see note)	See Table 9.8-2 for time points of collection. Samples may be collected within 3 days prior to dosing.

Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination)

	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)	Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D22 (± 3 days)**	**C2D1 and C2D22 (± 3 days)**	**C3D1 and Day 1 of each subsequent Cycle to EOT**[c] **(every 4 weeks) (± 3 days)**		
Collection of tumor tissue for biomarker research on-treatment and upon disease progression	C1D29-35 (1 week after 2nd dosing and before the 3rd dosing)				X (see note)	Tumor tissue submission while on-treatment (1 week after 2nd dosing and before the 3rd dosing, i.e. between Day 29-35 of Cycle 1) and upon progression (PD + 14 days) is optional but strongly recommended to understand the response/resistance to nivolumab plus ipilimumab treatment. See Table 9.8-2 for time points of collection. If biopsy or surgical resection is performed per protocol while on treatment or at progression (PD + 14 days), a tumor sample (block [preferred] or slides) should be submitted to central laboratory. If biopsies/ surgical resection are done at any other time on treatment, tissue samples should be submitted as well.
Clinical Drug Supplies						
Randomization	X					
IRT Drug Vial Assignment						Participant must receive the first dose of study medication within 3 days after randomization.
Nivolumab 240 mg flat dose IV	X	X	X			
Ipilimumab (1 mg/kg) IV	X	X	X			
Nivolumab 480 mg flat dose IV				X		

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

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

[c] Treatment to progression, unacceptable toxicity, withdrawal of consent, or maximum treatment duration as specified in Section 7.1.1

[d] Any additional imaging, including unscheduled timepoints, that may demonstrate tumor response/progression should be submitted to BICR.

[e] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review, BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CR29 Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-3L Questionnaire, EuroQol Five-Dimensional Questionnaire, Three-Level Questionnaire; FFPE, formalin-fixed paraffin-embedded; HCG, human chorionic gonadotropin; HR, heart rate; IgG, immunoglobulin G; IHC, immunohistochemistry; IRT, Interactive Response system; MDSC, myeloid-derived suppressor cell; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; PBMC, peripheral blood mononuclear cell, PCR, polymerase chain reaction; PK, pharmacokinetic; PD, progressive disease; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child bearing potential.

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
Safety							
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	X	Weight, BP, HR, temperature and Performance Status (see Appendix 6). Obtain prior to each dose.
Review of Concomitant Medications and Vaccination	Continuously					X	Record at each visit.
AE Assessment (including SAE Assessment)	Continuously					X	Record at each visit. All AEs (SAEs or non-serious AEs) must be collected continuously during the treatment period.
Clinical Laboratory Tests (CBC w/differential, Chemistry)	X	X	X	X	X		On site/ local laboratory testing should be done within 72 hours prior to each dose. Screening labs are acceptable if performed within the previous 72 hours and results are available. For full list of assessments to be performed, see Section 9.4.4

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
Urinalysis	X[d]	X[d]	X[d]	X[d]	X[d]		For participants assigned to receive bevacizumab-containing regimens only.
CEA and CA19-9 Assessment	X	X (see note)				X	CEA alone or CEA and CA19-9 will be assessed prior to each restaging (every 6 weeks (± 7 days) for the first 24 weeks, and every 8 weeks (± 7 days) thereafter). Sample collection can be obtained at the corresponding dosing visit.
Pregnancy Test (WOCBP only)	X	C1D29	C2D15	X (see note)			Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
Health Outcomes							
EORTC QLQ-C30 Questionnaire	X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
EORTC QLQ-CR29	X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs
EQ-5D-3L Questionnaire	X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1 and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
							with when that time point's dosing actually occurs
Efficacy Assessments							
Tumor assessments[e]	See note						**During first 96 weeks from randomization (Year 1 and 2)** Tumor assessment should occur every 6 weeks (± 7 days) from randomization for the first 24 weeks, and every 8 weeks (± 7 days) thereafter, until BICR confirmed progression, and treatment discontinuation (including treatment beyond progression), whichever occurs later. This schedule should be followed even if treatment delay occurs. See Section 9.1.1 for further details. **During week 97 - 144 from randomization (Year 3)** Tumor assessment should occur every 16 weeks (± 7 days) until BICR confirmed progression. See Section 9.1.1 for further details. **Beyond week 144 from randomization (Year 4 and beyond)**

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
							Tumor assessment should occur every 24 weeks (± 14 days) until BICR confirmed progression. See Section 9.1.1 for further details.
Brain Imaging			See note				Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). See Section 9.1.1 for further details.
Other Imaging (eg, Bone Scan)			See note				As clinically indicated per local standards. See Section 9.1.1 for further details.
Biomarker Assessments							
Exploratory Plasma Biomarkers, Whole Blood DNA, MDSC, PBMC, Serum	X		X (see note)			X (see note)	See Table 9.8-1 for time points of collection.

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
SARS-CoV-2 Serology[f]		X (See note)					Serum collected approximately every 6 cycles during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3]).
Stool samples for microbiome analysis	C2D1					X (see note)	See Table 9.8-1 for time points of collection. Samples may collected within 3 days prior to dosing.

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
Collection of tumor tissue for biomarker research on-treatment	C1D22-28 (1 week after 2nd dosing and before the 3rd dosing)					X (see note)	Tumor tissue submission while on-treatment (1 week after 2nd dosing and before the 3rd dosing, i.e. between Day 22-28 of Cycle 1) and upon progression (PD + 14 days) is optional but strongly recommended to understand the response/resistance to nivolumab treatment. See Table 9.8-1 for time points of collection. Tumor tissue collection upon progression (PD + 14 days) is mandatory if medically feasible for enrolment to Crossover Cohort. If biopsy or surgical resection is performed per protocol while on treatment or at progression, a tumor sample (block [preferred] or slides) should be submitted to central laboratory. If biopsies/ surgical resection are done at any other time on treatment, tissue samples should be submitted as well.
Clinical Drug Supplies							
Randomization	X						

Table 2-4: On Treatment Procedural Outline (CA2098HW) Arm C (Investigator's Choice Chemotherapy)

	Cycles 1 and 2 (cycle =6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]	**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15, and C2D29 (± 3 days)**	**C3D1, and Day 1 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**	**C3D15, and Day 15 of each subsequent Cycle to EOT[c] (every 4 weeks) (± 3 days)**		
IRT Drug Vial Assignment							Participant must receive the first dose of study medication within 3 days after randomization.
Oxaliplatin, 85 mg/m^2	X (see note)						Chemotherapy drugs will be administered every 2 weeks per local standards. See Section 7.1.2 for details.
Leucovorin, 400 mg/m^2							
Fluorouracil bolus, 400 mg/m^2							
Fluorouracil infusion, 2400 mg/m^2							
Irinotecan, 180 mg/m^2							
Bevacizumab, 5 mg/kg							
Cetuximab, 500 mg/m^2							

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

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

[c] Treatment to progression, unacceptable toxicity, withdrawal of consent, or maximum treatment duration as specified in Section 7.1.1

[d] If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis a 24 hour urine collection or UPCR should be performed and results obtained before the next treatment with bevacizumab. See Sections 7.4.1.2 (Dose Delay), 7.4.2.2 (Dose Reductions), and 7.4.5 (Criteria to Resume Treatment) for bevacizumab dose modification criteria.

[e] Any additional imaging, including unscheduled timepoints, that may demonstrate tumor response/progression should be submitted to BICR.

[f] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review, BP, blood pressure; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CR29 Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-3L Questionnaire, EuroQol Five-Dimensional Questionnaire, Three-Level Questionnaire; FFPE, formalin-fixed paraffin-embedded; HCG, human chorionic gonadotropin; HR, heart rate; IgG, immunoglobulin G; IHC, immunohistochemistry; IRT, Interactive Response system; MDSC, myeloid-derived suppressor cell; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; PBMC, peripheral blood mononuclear cell, PCR, polymerase chain reaction; PD, progressive disease; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of child bearing potential.

Table 2-5: Follow-Up Assessments (CA2098HW)

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes[c]
Safety Assessments			
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X		To assess for potential late emergent study drug related issues. Weight, BP, HR, temperature, and ECOG status. Targeted physical examination to be performed only as clinically indicated.
Adverse Events Assessment (Including SAE)	X	*	All AEs to be collected for 100 days after last dose of study treatment. Participants in arm C eligible to crossover have to complete at least Follow Up Visit 1 before entering the Crossover Cohort. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), for suspected cases, until SARS-CoV-2 is ruled out. *In Survival Follow-Up period only to include toxicities from study therapy.
ECG	X		Only at FU1. 12-lead ECG is required.
Review of Concomitant Medication and Vaccination	X		Only at FU1 except for Vaccination, that should be reviewed at both FU1 and FU2
Review of Subsequent Cancer Therapies	X	X	Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after second line therapy will be collected.
Laboratory Tests (CBC w/differential, Chemistry)	X		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. For full list of assessments to be performed, see Section 9.4.4.

Table 2-5: Follow-Up Assessments (CA2098HW)

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes[c]
Endocrine function testing	X (see note)		Thyroid function testing should be done. Additional tests (e.g. ACTH, cortisol, etc.) should be performed if clinically indicated. For participants who received nivolumab without or with ipilimumab. See Section 9.4.4
Urinalysis[d]	X (see note)		For participants who received bevacizumab
Pregnancy Test (WOCBP only)	X (see note)		Serum or urine only for FU1, unless testing is required for a longer period, per local regulations.
SARS-CoV-2 serology[e]	X (see note)		Only at FU1: Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3])
Efficacy Assessments			
Tumor assessments[f]	**During first 96 weeks from randomization (Year 1 and 2)** Participants who enter the follow-up period without BICR confirmed tumor progression will continue to have tumor imaging assessments as per on-treatment schedule (every 6 weeks [± 7 days] from randomization for the first 24 weeks, and every 8 weeks[g] [± 7 days] thereafter, until BICR confirmed disease progression, lost to follow-up, or withdrawal of consent, whichever occurs first. See Section 9.1.1 for details on methodology. **During week 97 - 144 from randomization (Year 3)** Tumor assessment should occur every 16 weeks (± 7 days) until BICR confirmed progression. See Section 9.1.1 for further details. **Beyond week 144 from randomization (Year 4 and beyond)** Tumor assessment should occur every 24 weeks (± 14 days) until BICR confirmed progression. See Section 9.1.1 for further details.		
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks) or sooner if clinically indicated. See Section 9.1.1 for further details.		
Other Imaging (eg. Bone Scan)	As clinical indicated per local standards. See Section 9.1.1for further details.		

Table 2-5: Follow-Up Assessments (CA2098HW)

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes[c]
TSST/PFS2 assessment	X	X	Following first progression, participants will continue to be followed during the safety and survival visits. Timing of second progression per Investigator's assessment will be documented.
Outcomes Research Assessment			
EQ-5D-3L Questionnaire	X	X	Can be collected either during a clinic visit or by telephone.
EORTC QLQ-C30	X		
EORTC QLQ-CR29	X		
Participant Status			
Survival Status[b] and Subsequent Therapy Information	X	X	Every 3 months after safety follow-up Visit 2; may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy after completing safety follow up visit. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression after subsequent line therapy will be collected.

[#] **Follow Up assessments are applicable for participants entering the Follow Up phase from arms A, B and C (first treatment Follow Up), and from the Crossover Cohort (second treatment Follow Up).** Follow Up visits 1 (FU1) and 2 (FU2) are in-clinic visits. Follow-up visit 1 (FU1) occurs approximately 30 days after the last dose (± 7 days) or coincides with the date of discontinuation (± 7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) occurs approximately 100 days (± 7 days) from last dose. Both Follow Up visits should be conducted in person.

[a] All participants must be followed for at least 100 days after last dose of study treatment with the exception of participants from arm C that experience PD on treatment AND who enter the Crossover Cohort. These participants are required to complete at least Follow Up Visit 1 following EOT in arm C.

[b] Survival Follow Up Visits may be conducted in clinic or via telephone contact: Every 3 Months (± 7 days) from FU2. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

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

[d] Urinalysis or urine dipstick. If blood, protein, or leukocytes esterase are positive on the dipstick, microscopic examination of the sediment is required. If urine protein is ≥ 2+ from urine dipstick or equivalent from random urinalysis, 24-hour urine collection or UPCR may be performed if deemed clinically indicated by the investigator.

[e] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

[f] Any additional imaging, including unscheduled timepoints, that may demonstrate tumor response/progression should be submitted to BICR.

[g] Every 12 weeks for participants who enter Follow Up from the Crossover Cohort.

Abbreviations: AE, adverse event; BP, blood pressure; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CR29 Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-3L Questionnaire, EuroQol Five-Dimensional Questionnaire, Three-Level Questionnaire; HR, heart rate; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PFS2, time from randomization to second disease progression or death; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSST, time from randomization to second subsequent therapy or death; WOCBP, women of child bearing potential.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
Eligibility assessment								
Informed consent	X							
Eligibility criteria	X							Participants must have completed Follow-Up Visit 1 on arm C, meet all eligibility criteria for crossover to nivolumab plus ipilimumab therapy (See Section 6.3), and have had a tumor biopsy upon progression on arm C, if medically feasible.
Safety Assessments								
Targeted Physical Examination, Physical Measurements, Vital Signs, ECOG Performance Status	X	X	X	X	X	X**	X	**Baseline visit**: Must be collected within 14 days prior to vial assignment. Weight, BP, HR, temperature and Performance Status (see Appendix 6). Obtain prior to each dose. **Only on days when ipilimumab is administered.
ECG	X							Within 14 days prior to vial assignment. 12-lead ECG is required.
Review of Concomitant	X	Continuously					X	Record at each visit.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
Medications and Vaccination								
Adverse Events Assessment (including SAE Assessment)	X	Continuously					X	Record at each visit.
Clinical Laboratory Tests (CBC w/differential, Chemistry, Viral)	X (See note)	X	X	X	X	X**		**Baseline visit:** CBC with differential, chemistry must be performed within 14 days prior to vial assignment. Viral testing to be performed within 28 days prior to vial assignment. See Section 9.4.4 for the details. **On treatment visits:** On site/ local laboratory testing for CBC with differential and chemistry should be done within 72 hours prior to each dose. Baseline labs are acceptable if performed within the previous 72 hours and results are available. For full list of assessments to be performed, see Section 9.4.4 **Only on days when ipilimumab is administered.
Urinalysis	X (See note)							Testing must be performed within 14 days prior to vial assignment. See Section 9.4.4
Endocrine function testing	X (See note)	X	X (see note)					**Baseline visit:** Testing must be performed within 14 days prior to vial assignment. See Section 9.4.4

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		C1D1	C1D15 and C1D29 (± 3 days)	C2D1, C2D15 and C2D29 (± 3 days)	C3D1 and Day 1 of each cycle to EOT[c] (± 3 days)	C3D15 and Day 15 of each cycle to EOT[c] (± 3 days)		
								On-treatment visits: thyroid function testing should be done every 6 weeks for the first 24 weeks, and then every 8 weeks until completion of study treatment. If clinically indicated additional tests (ACTH, cortisol) to be performed per local requirements. See Section 9.4.4
CEA and CA19-9 Assessment	X	X	X (see note)				X	CEA alone or CEA and CA19-9 will be assessed prior to each restaging (every 6 weeks (± 7 days) for the first 24 weeks, and every 12 weeks (± 7 days) thereafter). Sample collection can be obtained at the corresponding dosing visit.
Pregnancy Test (WOCBP only)	X	X	X	X	X			Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at baseline visit and within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Health Outcomes								
EORTC QLQ-C30 Questionnaire		X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
								visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
EORTC QLQ-CR29 Questionnaire		X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
EQ-5D-3L Questionnaire		X		C2D1	See note			Assessed prior to dosing on C1D1, C2D1, C3D1, and then every other cycle (Q8W) thereafter. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the patient-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
Efficacy Assessments								
Tumor assessments[d]	X (see note)	See note						**Baseline**: The participant will be re-baselined based on the investigator's assessment of the scans with which BICR progression was determined. **During first 96 weeks from start of treatment in Crossover cohort (Year 1 and 2)** **On treatment:** Tumor assessment should occur every 6 weeks (± 7 days) from vial assignment for the first 24 weeks, and every 12 weeks (± 7 days) thereafter, until BICR confirmed progression, and treatment discontinuation (including treatment beyond progression), whichever occurs later. This schedule should be followed even if treatment delay occurs. See Section 9.1.1 for further details. **During week 97 - 144 from start of treatment in Crossover cohort (Year 3)** Tumor assessment should occur every 16 weeks (± 7 days) until BICR confirmed progression. See Section 9.1.1 for further details.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
								Beyond week 144 from start of treatment in Crossover cohort (Year 4 and beyond) Tumor assessment should occur every 24 weeks (± 14 days) until BICR confirmed progression. See Section 9.1.1 for further details.
Brain Imaging	X	See note						Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). See Section 9.1.1 for further details.
Other Imaging (eg, Bone Scan)	X	See note						As clinically indicated per local standards. See Section 9.1.1 for further details.
Pharmacokinetic /Immunogenicity Assessments								
PK and Immunogenicity samples		X	See note					See Table 9.5-3 for time points of collection.
Biomarker Assessments								
Exploratory Plasma Biomarkers, Whole Blood DNA,		X	See note				X (See note)	See Table 9.8-3 for time points of collection.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
MDSC, PBMC, Serum								
SARS-CoV-2 Serology[e]	X		X (see note)					**Baseline:** Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3]). **On treatment:** Serum collected approximately every 6 cycles during study treatment to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.3]).
Stool samples for microbiome analysis	X (See note)	C2D1 (See note)					X (See note)	See Table 9.8-3 for time points of collection. **Baseline visit**: Stool sample to be collected within 7 days prior to first dose. **On treatment visit**: Samples may be collected within 3 days prior to dosing.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT[c] (± 3 days)**	**C3D15 and Day 15 of each cycle to EOT[c] (± 3 days)**		
Collection of tumor tissue for biomarker research on-treatment and upon disease progression	X (See note)	C1D22-28 (1 week after 2nd dosing and before the 3rd dosing)					X (See note)	**Baseline visit**: Tumor biopsy upon progression on or after chemotherapy treatment in arm C is mandatory, if medically feasible, for enrollment to Crossover Cohort. **On treatment visits**: Tumor tissue submission while on-treatment (1 week after 2nd dosing and before the 3rd dosing, i.e. between Day 22-28 of Cycle 1) and upon progression (PD + 14 days) is optional but strongly recommended to understand the response/resistance to nivolumab plus ipilimumab treatment. See Table 9.8-3 for time points of collection. If biopsy or surgical resection is performed per protocol while on treatment or at progression, a tumor sample (block [preferred] or slides) should be submitted to central laboratory. If biopsies/ surgical resection are done at any other time on treatment, tissue samples should be submitted as well.
Clinical Drug Supplies								
IRT	X							
IRT Drug Vial Assignment								Participant must receive the first dose of study medication within 3 days from drug vial assignment.

Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort

	Baseline	Cycles 1 and 2 (cycle = 6 weeks)			Cycle 3 to EOT (cycle = 4 weeks)		Upon PD	Notes
Procedure[a,b]		**C1D1**	**C1D15 and C1D29 (± 3 days)**	**C2D1, C2D15 and C2D29 (± 3 days)**	**C3D1 and Day 1 of each cycle to EOT**[c] **(± 3 days)**	**C3D15 and Day 15 of each cycle to EOT**[c] **(± 3 days)**		
Nivolumab 240 mg flat dose IV		X	X	X				
Ipilimumab (1 mg/kg) IV		X		C2D1 only	C3D1, C6D1, C9D1 and Day 1 of every 3 cycles	C4D15, C7D15, C10D15 and Day 15 of every 3 cycles		
Nivolumab 480 mg flat dose IV					X			

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

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

[c] Treatment to progression, unacceptable toxicity, withdrawal of consent, or maximum treatment duration as specified in Section 7.1.1

[d] Any additional imaging, including unscheduled timepoints, that may demonstrate tumor response/progression should be submitted to BICR.

[e] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Abbreviations: AE, adverse event; CA19-9, cancer antigen 19-9; CBC, complete blood count; CEA, carcino embryonic antigen; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CR29 Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29;

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-3L Questionnaire, EuroQol Five-Dimensional Questionnaire, Three-Level Questionnaire; IgG, immunoglobulin G; IRT, Interactive Response system; MDSC, myeloid-derived suppressor cell; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PFS2, time from randomization to second disease progression or death; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSST, time from randomization to second subsequent therapy or death; WOCBP, women of child bearing potential.

3 INTRODUCTION

3.1 Study Rationale

CA2098HW (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation [CHECKMATE]-8HW) is a Phase 3, randomized open-label multi-center 3-arm clinical trial of nivolumab monotherapy, nivolumab plus ipilimumab combination therapy or standard chemotherapy in recurrent or metastatic dMMR/MSI-H (see Appendix 1 for List of Abbreviations) CRC across all lines of therapy.

Results from non-randomized cohort study CA209142 led to the accelerated approval of nivolumab single agent or in combination with ipilimumab for dMMR/MSI-H metastatic CRC (mCRC) patients who progressed after fluoropyrimidine, oxaliplatin, and irinotecan treatment. Although both nivolumab monotherapy and nivolumab plus ipilimumab combination therapy demonstrated strong clinical activity, indirect comparisons suggested improved clinical benefit of combination therapy versus monotherapy. The CA2098HW is designed to confirm these findings and directly compare the clinical benefit, as measured by PFS, ORR and OS, achieved by nivolumab in combination with ipilimumab or by nivolumab monotherapy.

It is generally accepted that patients with dMMR/MSI-H metastatic CRC are less responsive to conventional chemotherapy and may have a poorer prognosis than patients with mismatch repair-proficient (pMMR) or MSS mCRC. Studies comparing single agent immunotherapy vs chemotherapy in patients who have not received prior treatment are currently ongoing, however there are no randomized studies evaluating combination of immunotherapies vs chemotherapy. Recently presented data from a randomized phase 3 study comparing pembrolizumab with standard chemotherapy in front-line setting (Keynote-177 study) confirmed superior antitumor activity as reflected by PFS and ORR achieved by anti-PD1 single agent vs chemotherapy in MSI-H mCRC patients.[1] In the CA209142 study, nivolumab plus ipilimumab combination in previously untreated dMMR/MSI-H mCRC patients demonstrated a high ORR and durable responses which translated into improvement of PFS and OS. Also, this combination showed favorable safety profile. Promising activity of nivolumab plus ipilimumab combination as 1L treatment in dMMR/MSI-H mCRC patients requires further evaluation, including direct comparison vs chemotherapy, a current standard of care. This will be evaluated in CA2098HW study.

The CA2098HW study also includes a pharmacodiagnostic component as part of a post-approval commitment in the US. The study data will be utilized to support the analytical and clinical validation of an immunohistochemistry-based (IHC) and a nucleic acid-based (PCR) in vitro diagnostic device that is essential to the safe and effective use of nivolumab and/or nivolumab plus ipilimumab combination therapy for patients with tumors that are dMMR/MSI-H.[2, 3]

3.1.1 Research Hypothesis

CA2098HW study will test 3 research hypotheses. The first hypothesis is that nivolumab plus ipilimumab combination therapy will improve PFS when compared with nivolumab monotherapy in participants with recurrent or metastatic dMMR/MSI-H CRC across all lines of therapy. This hypothesis will be evaluated across participants randomized to nivolumab monotherapy or

nivolumab plus ipilimumab combination therapy. The second hypothesis is that nivolumab plus ipilimumab combination therapy is superior to standard chemotherapy as measured by PFS in participants with recurrent or metastatic dMMR/MSI-H CRC who have not received prior treatment for metastatic disease. The second hypothesis will be assessed across all study participants who have not received prior therapy (1L) and were randomized to nivolumab plus ipilimumab combination therapy or standard chemotherapy arms. The third research hypothesis is that nivolumab plus ipilimumab combination improves PFS compared with nivolumab monotherapy in participants who have not received prior therapy (1L). This hypothesis will be tested hierarchically.

3.2 Background

3.2.1 Metastatic Colorectal Cancer

Colorectal cancer is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease.[4,5] The active agents in first- and second-line treatment of mCRC consist of fluoropyrimidines (5-FU, capecitabine), oxaliplatin, and irinotecan. Chemotherapy is often combined with a monoclonal antibody inhibiting VEGF (bevacizumab or ziv-aflibercept); or EGFR (cetuximab or panitumumab; only indicated in RAS wild-type tumors). Despite newer treatment options for mCRC, the benefit of systemic therapy after first-line treatment is modest, and complete responses are rare. The multi-targeted tyrosine kinase inhibitor, regorafenib, and the oral nucleoside analogue trifluridine/tipiracil (TAS-102) are among more recently available options beyond second line. For unselected patients with refractory mCRC, accumulating data seem to support the use of these agents prior to considering "rechallenge" with a previously used agent.[6] Regorafenib and trifluridine/tipiracil seem to have similar efficacy in the refractory setting with different toxicity profiles. The OS and DCR are improved with both of these agents compared to placebo, however response rates seem to be very low (1-4%).[7,8,9,10] In the pivotal study of regorafenib vs placebo (CORRECT study) the median OS and PFS was 6.4 months and 1.9 months in regorafenib arm, and 5 months and 1.7 months in placebo arm, respectively.[7] In the Phase 3 study of TAS-102 in refractory mCRC the median OS improved from 5.3 months with placebo to 7.1 months with TAS-102. The median PFS improved from 1.7 months in placebo arm to 2 months in TAS-102 arm.[10]

Colorectal cancer is shown to be a heterogeneous disease at the molecular level. [11] A comprehensive and globally accepted disease classification system has not yet been established in terms of optimizing personalized medicine. However, there are few established biomarkers that provide predictive and prognostic information. Clinical practice in many centers have rapidly evolved to include assessment of key biomarkers in clinical decision making, including testing for KRAS, NRAS, BRAF mutations, and evaluation of MMR or MSI status, by IHC or by PCR, respectively. Among these, dMMR/MSI-H status in metastatic CRC has both prognostic and predictive value. Patients with m dMMR/MSI-H CRC have a worse outcome when treated with SOC, yet they may have potential durable benefit if treated with checkpoint inhibitors.

3.2.2 Microsatellite Instability and Metastatic Colorectal Cancer

Microsatellite instability is the molecular fingerprint of a deficient mismatch repair, which is involved in CRCs arising in association with Lynch syndrome as well as subgroup of sporadic CRC. The term MSI is widely accepted as a surrogate for both dMMR and MSI-H tumors. These are characterized by either epigenetic silencing of MLH1 or a germline mutation in one of the mismatch repair genes MLH1, MSH2, MSH6, or PMS2.[12] There are well established methods to detect dMMR/MSI-H that are incorporated into clinical practice.

Studies have shown that dMMR/MSI-H CRC seems to be clinically distinct from MSS/pMMR CRC. Approximately 15% of patients with stage II or stage III CRC have dMMR/MSI-H tumors. While patients with stage II dMMR/MSI-H CRC might not benefit from adjuvant 5-FU-based adjuvant chemotherapy, overall patients with non-metastatic dMMR/MSI-H CRC seem to have better prognosis than non-MSI-H/proficient MMR CRC.[13,14] However, patients with metastatic dMMR/MSI-H CRC, (approximately 5% of all mCRC), have been reported to have a worse OS, and seemingly less benefit from conventional chemotherapy.[15,16,17,18]

A pooled analysis of four Phase 3 studies in first-line mCRC participants treated with chemotherapy demonstrated that median PFS (6.2 months vs 7.6 months) and OS (13.6 months vs 16.8 months) were significantly worse for patients with dMMR compared with pMMR tumors, respectively.[16] In later lines of treatment an exploratory retrospective analysis of a small subgroup of MSI-H patients treated with regorafenib or placebo on CORRECT trial failed to show an interaction between MSI status and regorafenib treatment benefit in OS or PFS, however there was less clinical benefit in patients with MSI-H subgroup.[19] A recent South Australian registry analysis of patient characteristics and survival outcomes compared patients with MSI-H or MSS disease. There was a trend towards poorer outcomes in MSI-H mCRC and this was considered to point towards the need for alternate treatment approaches. [20]

3.2.3 Chemotherapy and Targeted Agents in dMMR/MSI-H Metastatic Colorectal Cancer

Current Standard of Care (SOC) for patients with dMMR/MSI-H mCRC who have not received any prior systemic therapy (1L) or who have received one prior line of systemic therapy (2L) consists of combination of cytotoxic agents that are frequently used together with anti-VEGF or -anti-EGFR antibodies. These combinations are referred as chemotherapy. Although available first-line therapies are effective, there remains an unmet need for therapies that will result in durable responses and survival.

Currently there are no randomized prospective studies on the efficacy and safety of chemotherapy compared with immunotherapy in dMMR/MSI-H mCRC patients. Currently available data for patients with dMMR/MSI-H consist of post-hoc analyses of the randomized clinical studies, meta-analyses of clinical trials, or retrospective cohort studies conducted on unselected mCRC patients. Importantly, in dMMR/MSI-H mCRC tumors the data on efficacy of chemotherapy are primarily available for 1L patients and these data are described further. To evaluate the efficacy of chemotherapy in dMMR/MSI-H mCRC patients Koopman et al. (2009) conducted a retrospective

analysis of CAIRO study to compare the PFS/OS results in patients with dMMR and pMMR tumors receiving 1L treatment. The tumor tissues were available from 515 patients with advanced mCRC of which 18 had dMMR/MSI-H status. The investigators found a non-significant decrease in median OS of 17.9 vs 10.2 months, and in median PFS of 6.9 vs 4.0 months in pMMR vs dMMR patients treated with chemotherapy, with a decreased disease control rate of 83 vs 56%, respectively. These results were supported by the meta-analysis of the 4 studies that included primary tumors from 3,063 patients. The median PFS (6.2 months vs 7.6 months) and OS (13.6 months vs 16.8 months) was significantly shorter in dMMR/MSI-H patients compared with MSS patients treated with chemotherapy.

Recently post-hoc analyses of patients with dMMR/MSI-H mCRC treated with 1L chemotherapy on CALBG/SWOG80405 and FIRE-3 studies, were published.[18, 21] These data should be interpreted with caution considering small number of patients with dMMR/MSI-H mCRC in both studies. CALBG/SWOG80405 study compared 1L bevacizumab vs cetuximab co-administered with FOLFOX or FOLFIRI, and FIRE-3 trial compared bevacizumab vs cetuximab both co-administered with FOLFIRI in RAS wild type mCRC. In CALBG/SWOG80405 study mPFS and mOS were respectively 9.3 and 30 months in bevacizumab treated; 5.4 and 11.9 in cetuximab treated dMMR/MSI-H mCRC patients. These data pose a question on potential resistance of dMMR/MSI-H mCRC to Cetuximab. Analysis of FIRE-3 trial by Consensus Molecular Sub-type (CMS) showed no difference in PFS or OS for cetuximab vs bevacizumab added to FOLFIRI in patients with CMS-1 (data was reported for CMS-1 due to small number of dMMR/MSI-H patients). Therefore survival data were combined across both bevacizumab and cetuximab arms. In CMS-1 RAS wild type mCRC patients' mPFS and OS were, respectively, 7.8 and 14.8 month; while in CMS-1 RAS mutant mCRC patients' mPFS and OS were, respectively, 9.6 and 17.4 month.

Limited data in second-line setting show shorter PFS in dMMR/MSI-H mCRC patients compared to pMMR/MSS patients. The retrospective analysis of the dMMR/MSI-H cohort from 18 centers in France reported the mPFS of 3.5 months, and the OS of 15.8 months.[22]

Some 30-40% of patients with dMMR/MSI-H mCRC harbor BRAF V600E mutation associated with poor outcomes. Recently, data from a study for BRAF mutant mCRC (Beacon-CRC study) that allowed to enroll patients with dMMR/MSI-H tumors, have been published. Beacon-CRC study compared efficacy and safety of encorafenib, binimetinib, and cetuximab (triplet-therapy group); encorafenib and cetuximab (doublet-therapy group); or chemotherapy (control group - cetuximab and irinotecan or cetuximab and FOLFIRI) in mCRC patients who have disease progression after one or two previous regimens. Proportion of dMMR/MSI-H patients was low across all study groups - 10%, 9% and 5% in triplet, doublet and control group, respectively. The ORR were 26% in triplet group, 20% in doublet group and 2% in control group. Duration of response at least 6 months was reported in 24% (7/29) of patients in triplet group, 43% (10/23) in doublet group and 50% (1/2) in control group. Responses were not durable due to resistance development. Median PFS and OS were respectively 4.3 and 9 months with triplet regimen; 4.2 and 8.4 months with doublet regimen; 1.5 and 5.4 months with chemotherapy. Consistently with the overall population, patients with dMMR/MSI-H tumors demonstrated improved survival in

triplet therapy group, though confidence interval was broad and crossed 1 (HR = 0.67 (95% CI, 0.26 to 1.76)).

3.2.4 Immunotherapy in dMMR/MSI-H Metastatic Colorectal Cancer: Check-Mate-142 Study and Other Data

The strong local immune reaction observed in dMMR/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 dMMR/MSI-H CRC might lead to the generation of tumor-specific antigens. The existence of T cell responses directed against multiple tumor antigens in individuals with dMMR/MSI-H CRC has been demonstrated in patients.[26,27] 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. In study CA209-003, a Phase 1 trial of nivolumab in participants with solid tumors, one trial participant with dMMR/MSI-H mCRC had a long-term complete response, suggesting the immune-modulatory approach warranted further evaluation.[28] These findings led to the CA209142 study in dMMR/MSI-H mCRC.

The initial results of CA209142 showed efficacy of nivolumab monotherapy in a cohort of 74 patients previously treated with, or intolerant of one or more prior lines of therapy.[29] Durable clinical benefit and deepening of responses were demonstrated with long term follow up. At a median follow up of 21 months (17-40 months), ORR and DCR per BICR was 34% and 62%, respectively. The CRs increased to 9% after median follow up of 21 months from 3% reported after median follow up period of 12 months[30]. No new safety signals were reported with long-term follow-up. Grade 3 to 4 treatment-related AEs were reported in 20% of patients.

In another cohort of CA209142, safety and efficacy of nivolumab plus ipilimumab combination were evaluated in 119 patients with dMMR/MSI-H mCRC. As in the nivolumab monotherapy cohort, the nivolumab plus ipilimumab cohort enrolled patients who were previously treated with, or intolerant of one or more prior lines of therapy. Patients received nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) every 3 weeks for four doses followed by the same dose of nivolumab every 2 weeks until disease progression or discontinuation for other reasons. At a median follow up of 13.4 months (range: 9-25 months) the ORR and DCR per BICR were reported in 49% (n=58) and 81% (n=97), respectively.[31] Grade 3 to 4 treatment-related AEs occurred in 32% of patients and were manageable. Patients (13%) who discontinued treatment because of study drug-related AEs had an ORR (63%) consistent with that of the overall population.

High rates and durability of responses observed with both nivolumab monotherapy and nivolumab plus ipilimumab combination translated into clinical benefit in dMMR/MSI-H mCRC as measured by PFS and OS. Median PFS per BICR in the nivolumab monotherapy cohort was 6.6 months, and not reached in the nivolumab plus ipilimumab cohort. The OS was not reached in either cohorts. Indirect comparisons of the data with similar follow up period, suggest that combined immunotherapy using ipilimumab and nivolumab provides improved efficacy over nivolumab monotherapy and has a favorable benefit-risk ratio.

Based on these results, the US FDA granted an accelerated approval for nivolumab monotherapy (31-Jul-2017) and nivolumab combination with ipilimumab (10-Jul-2018) in dMMR/MSI-H mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The safety and efficacy of nivolumab plus ipilimumab combination in 1L setting was assessed in Cohort 3 of CA209142 study. In a 1L cohort of CA209142 study 45 previously untreated for metastatic disease patients with histologically confirmed metastatic or recurrent CRC and dMMR/MSI-H status per local laboratory, received nivolumab 3 mg/kg administered every 2 weeks (Nivo 3 Q2W) plus ipilimumab 1 mg/kg administered every 6 weeks (Ipi 1 Q6W). After median follow up of 19.9 months (range: 15.1 - 24.6), BICR-assessed ORR was 58%; 78% of patients had disease control for ≥ 12 weeks. Responses were consistent with the overall population across evaluated subgroups including age, gender, ECOG performance status, primary tumor location, mutation status, and prior adjuvant/neoadjuvant therapy. At 15 months, PFS and OS rates (95% CI) per investigator assessment were 75% (59–85) and 84% (70–92), respectively. No new safety signals were reported. Overall, 20% of patients had grade 3–4 treatment related adverse event (TRAEs). TRAEs of any grade led to discontinuation in 5 (11%) patients.[32]

Efficacy and safety of pembrolizumab in MSI-H mCRC patients were demonstrated in several clinical studies in previously treated patients leading to accelerated approval in the US for MSI-H mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Recently, the results of the trial comparing pembrolizumab with chemotherapy as 1L treatment have been disclosed. Pembrolizumab demonstrated superior activity as reflected by doubling of mPFS (16.5 vs 8.2 months), higher rates of response (43.8% vs 33.1%), and its durability (median not reached vs 10.6 months).[1]

In the US, the NCCN panel recommends nivolumab (alone or in combination with ipilimumab), or pembrolizumab as a treatment option in first-line for patients who are not appropriate for intensive chemotherapy (category 2B), and for all patients with dMMR/MSI-H mCRC beyond first-line (category 2A).[33] The NCCN also recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to inform the use of immunotherapy in metastatic disease. While such testing is also done in many parts of the world and the importance of the checkpoint inhibitor approach for this population is scientifically recognized, nivolumab in combination with ipilimumab does not carry this indication in the rest of the world at this time.

3.2.5 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[34,35,36] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by mechanisms such as introducing cancer antigens by therapeutic

vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[37] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[38] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ, and Bcl-xL. PD-1 expression has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[39] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMab; immunoglobulinG4 [IgG4]-S228P). Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA 4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a CMV re-stimulation assay with PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[40]

3.2.6 *Ipilimumab Mechanism of Action*

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[41] Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.7 *Nivolumab Combined with Ipilimumab: Clinical Activity Across Different Tumor Types*

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules.

The following information describes the results of initial early phase clinical studies that were the basis for the nivolumab plus ipilimumab combination regimens that have been explored in late phase clinical development.

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

Of the 52 participants evaluable for response as of the 15-Feb-2013 clinical cut-off in CA209004, 21 participants (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 participants (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable participants had an objective response by mWHO (21%), including 1 CR and 2 PRs.[42] In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 (53%) evaluable participants had an objective response by mWHO, including 3 CRs (18%) and 6 PRs (35%). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 (40%) response evaluable participants had an objective response by mWHO, including 1 CR (7%) and 5 PRs (33%). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 (50%) evaluable participants had an objective response by mWHO, all 3 of which were PRs (50%).

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

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

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

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.[42,43]

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

Participants were randomized to N3 + I1 (n = 47) and N1 + I3 (n = 47). Approximately half (n = 48; 51%) had prior systemic therapy (N3 + I1: 22; N1 + I3: 26). After a median follow-up of 22.3 months, the confirmed ORR per RECIST 1.1 was 40.4% (n = 47) in both arms N3 + I1 and N1 + I3; 42.1% (n = 8) and 36.8% (n = 7) had an ongoing response, with a median DOR of 88.7 weeks (95% CI: 37.14, NA) and 85.9 weeks (95% CI: 35.14, NA), respectively. Median PFS was 7.7 months (95% CI: 3.71, 14.29) and 9.4 months (95% CI: 5.62, 18.63) in arms N3 + I1 and N1 + I3, respectively. OS at 12 months was 80.9% and 85.0% in arms N3 + I1 and N1 + I3, respectively, and at 24 months was 67.3% and 69.6%, respectively.

Treatment-related AEs were seen in 88/94 pts (94%), including 43/47 (92%) in N3 + I1 and 45/47 (96%) in N1 + I3. The most frequently reported drug-related AEs in N3 + I1 included fatigue (66%), cough (53.2%), and arthralgia (51.1%); the majority were Grade 1- 2. The most frequently reported drug-related AEs in N1 + I3 included fatigue (74.5%), nausea (55.3%), and diarrhea (53.2%). The majority were Grade 1-2. Treatment-related AEs leading to discontinuation (31.9% versus 10.6%), and treatment-related SAEs (34% versus 23.4%) occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm, respectively.[44,45]

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

The rate of treatment-related AEs in the N+I Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3/4 AEs were 37%, 33%, and 19% for the N+I Q12W, Q6W and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-

related select AEs in patients administered the optimized dosing schedule (3 mg/kg of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related Grade 3 and Grade 4 AEs per category.[46]

CA209067 was a Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in first-line melanoma patients. In this study, combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg for 4 doses, followed by nivolumab 3 mg/kg, Q2W (N+I), compared with ipilimumab 3 mg/kg, Q3W x4 doses (Ipi) demonstrated a significant improvement in OS and PFS. Median OS not reached in the N+I group compared with 19.98 months in the Ipi group, and mPFS was 11.7 months in the N+I group compared with 2.9 months in the Ipi group. When N+I group was compared to nivolumab 3 mg/kg group (Nivo), a numeric difference in OS and improved PFS (mPFS of 11.73 vs 6.87 months) were observed in favor of the combination. The ORR in N+I (58.9%) was significantly higher than the Ipi group (19.0%) and numerically higher than N group (44.6%). The overall safety profile of N+I combination therapy and Nivo monotherapy was consistent with the mechanisms of action of nivolumab and ipilimumab. In general, the frequency of AEs was lowest across AE categories in the Nivo group and highest in the N+I group. Treatment-related AEs of Grade 3 or 4 occurred in 59% patients of the N+I group, 21% of the Nivo group and 34% of the Ipi group. Analyses of IMAEs showed that most IMAEs were Grade 1-2. The majority of IMAEs in the IMAE categories of diarrhea/colitis, and hepatitis were Grade 3-4. The majority of IMAEs resolved and were manageable using the recommended treatment guidelines for early evaluation and intervention[47].

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

3.3 Benefit/Risk Assessment

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

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. Additionally, the on-going CA209142 study provides mature efficacy data that confirms the overall positive benefit-risk assessment of both nivolumab and nivolumab plus ipilimumab combination in patients with dMMR/MSI-H mCRC.

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

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

The benefit and risk of front-line and second-line chemotherapy (FOLFOX or FOLFIRI without or with bevacizumab or cetuximab) has been well defined in clinical trials. Grade 3 to 5 AEs are common (up to 67%) particularly when cytotoxic agents (FOLFOX or FOLFIRI) are combined with targeted agents (bevacizumab, cetuximab, other). Most common Grade 3-5 AEs reported for chemotherapy + bevacizumab or cetuximab combinations are hematologic adverse events (approx. 30%), diarrhea (approx. 10%), and sensory neuropathy (approx. 13%). Other Grade 3-4 AEs include skin reactions that are commonly observed with cetuximab (up to 26%), while bevacizumab-containing regimens are associated with higher rate of bleeding (2%), gastrointestinal perforation (2%), and venous thromboembolic events (5%). Toxicities lower than grade 3 are distinct between these 2 targeted agents, with acneiform rash (61% vs 8%) predominating for cetuximab and hypertension (32% vs 15%) predominating for bevacizumab.[48,49]

4 OBJECTIVES AND ENDPOINTS

The study includes two target populations and objectives are set up according to the populations. The randomized participants regardless of prior lines of therapy will refer to ‘All lines’ and the randomized participants who have not received prior therapy for metastatic disease will refer to ‘1L’.

Primary Objective	**Endpoint**
• **All lines**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B vs A)
• **1L**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR (arm B vs C)

Secondary Objective	Endpoint
• **All lines**	
To compare the BICR assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	ORR by BICR (arm B vs A)
To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	OS (arm B vs A)
To estimate the Investigator-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by Investigator assessment (arm A and B)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who were randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR among all randomized participants (arm A and B)
• **1L**	
To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B vs A)
To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	ORR by BICR (arm B vs C)
To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	ORR by BICR (arm B vs A)
To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	OS (arm B vs A)
To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm	PFS by BICR (arm A and C)
To estimate the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	OS (arm B and C)
To estimate the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm	ORR by BICR (arm A and C)
To estimate the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab monotherapy arm or chemotherapy arm	OS (arm A and C)

Secondary Objective	Endpoint
To estimate the Investigator-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy by treatment arm	PFS by Investigator (arm A, B and C)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR among all randomized participants who have not received prior treatment (arm B and C)
To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR among all randomized participants who have not received prior treatment (arm A and B)
• **CDx (All lines and 1L)**	
To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm	PFS by BICR (arm B and C)
To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm	PFS by BICR (arm B and A)
• **Crossover Cohort**	
To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort	PFS by BICR
To estimate the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort	ORR by BICR

Exploratory Objective	Endpoint
To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have received 1 prior line by treatment arm	PFS by BICR (arm A, B and C)
To further define the safety and tolerability of study treatment in all treated dMMR/MSI-H mCRC participants by treatment arm and line of prior therapy	Including but not limited to: AEs/SAEs by grade and attribution, laboratory abnormalities (arm A, B and C)
To estimate the Investigator-assessed PFS during next line of treatment (PFS2) in randomized dMMR/MSI-H mCRC participants with centrally confirmed dMMR/MSI-H status per treatment arm	PFS2 by Investigator assessment (arm A, B and C)
To evaluate participant-reported symptoms, functioning, and quality of life in all randomized dMMR/MSI-H mCRC participants by treatment arm and line of prior therapy	EORTC QLQ-C30 and QLQ-CR29 scale and item scores and score changes
To evaluate participant-reported health status and utility in all randomized dMMR/MSI-H mCRC participants by treatment arm and line of prior therapy	EQ-5D-3L visual analog scale (VAS) and utility index scores and score changes

Exploratory Objective	Endpoint
To characterize the PK and the immunogenicity of nivolumab plus ipilimumab combination therapy and nivolumab monotherapy in all treated dMMR/MSI-H mCRC participants in nivolumab plus ipilimumab arm and in nivolumab monotherapy arm, respectively	Population PK parameters and incidence of immunogenicity for ipilimumab combined with nivolumab and nivolumab monotherapy (arm B and A)
To explore potential biomarkers associated with clinical efficacy in all randomized dMMR/MSI-H mCRC participants	Associations of select biomarkers that may include but not be limited to PD-L1, TMB and serum/plasma/microbiome biomarkers with efficacy outcomes (eg, OS, PFS and ORR)
To assess the time to treatment failure (TTF) across treatment arms in all randomized participants with centrally confirmed dMMR/MSI-H mCRC	TTF by Investigator assessment
To evaluate the recurrence free survival (RFS) after curative surgery by Investigator assessment in participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment by treatment arm	RFS by Investigator assessment
• **Crossover Cohort**	
To characterize the efficacy of nivolumab plus ipilimumab combination by line of prior therapy in participants treated in the crossover cohort as reflected by BICR-assessed ORR and PFS, and Investigator-assessed ORR, PFS and OS	ORR, PFS by BICR and Investigator assessment OS
To characterize the safety of nivolumab plus ipilimumab combination in participants treated in the Crossover cohort	Including but not limited to: AEs/SAEs by grade and attribution, laboratory abnormalities
To characterize the PK and the immunogenicity of nivolumab and ipilimumab in treated dMMR/MSI-H mCRC participants in the Crossover cohort	Population PK parameters and incidence of immunogenicity for ipilimumab combined with nivolumab

Main estimands for the primary and key secondary endpoints are summarized in Table 4-1.

Table 4-1: Main Estimands for the Primary and Key Secondary Endpoints

Endpoint	Population	Treatments	Intercurrent Events	Summary Statistics
PRIMARY OBJECTIVES				
PFS by BICR	All participants across lines who are randomized to Arm A and Arm B and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm A	• Death: composite variable strategy (eg, considered an event) • Start of subsequent therapy: while-on-	Stratified HR from CPH model, with CI

Table 4-1: Main Estimands for the Primary and Key Secondary Endpoints

Endpoint	Population	Treatments	Intercurrent Events	Summary Statistics
PFS by BICR	All participants in 1L who are randomized to Arm B and Arm C and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm C	treatment strategy (eg, PFS will be censored on the date of last evaluable tumor assessment prior to or on the same date of initiation of new anticancer therapy[a])	
KEY SECONDARY OBJECTIVES				
PFS by BICR	All participants in 1L who are randomized to Arm A and Arm B and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm A	• Death: composite variable strategy (eg, considered an event) • Start of subsequent therapy: while-on-treatment strategy (eg, PFS will be censored on the date of last evaluable tumor assessment prior to or on the same date of initiation of new anticancer therapy[a])	Stratified HR from CPH model, with CI
ORR by BICR	All participants across lines who are randomized to Arm A and Arm B and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm A	• Dropout or death without disease assessment: composite variable strategy (eg, included in the ORR analyses and categorized as nonresponders) • Start of subsequent therapy: while-on-treatment strategy (eg, only responses before the intercurrent event will be considered)	Difference of response rates using CMH method of weighting, with CI
ORR by BICR	All participants in 1L who are randomized to Arm B and Arm C and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm C		
ORR by BICR	All participants in 1L who are randomized to Arm	Arm B vs Arm A		

Table 4-1: Main Estimands for the Primary and Key Secondary Endpoints

Endpoint	Population	Treatments	Intercurrent Events	Summary Statistics
	A and Arm B and with centrally confirmed dMMR/MSI-H mCRC			
OS	All participants across lines who are randomized to Arm A and Arm B and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm A	• Lost to follow up: hypothetical strategy (eg, censor) • All other intercurrent events (eg, start of subsequent therapy) will be handled with treatment policy strategy (eg, OS will not be censored on the date of the initiation of subsequent anticancer therapy, assuming subsequent anticancer therapies represent clinical practice)	Stratified HR from CPH model, with CI
OS	All participants in 1L who are randomized to Arm B and Arm C and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm C		
OS	All participants in 1L who are randomized to Arm A and Arm B and with centrally confirmed dMMR/MSI-H mCRC	Arm B vs Arm A		

[a] For the endpoints of PFS per BICR, a supportive analysis will be performed using a treatment policy strategy to handle the intercurrent events of start of subsequent therapy. Under this strategy, information after the initiation of subsequent therapy will be used as well. Details are listed in statistical analysis plan.

Abbreviations: 1L, first line; BICR: Blinded Independent Central Review; CMH, Cochran-Mantel-Haenszel; CI, confidence interval; CPH, Cox proportional hazards; dMMR/MSI-H mCRC, DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer; HR, hazard ratio; ORR, overall responses rate; OS, overall survival; PFS, progression-free survival.

5 STUDY DESIGN

5.1 Overall Design

CA2098HW is a Phase 3, randomized, 3-arm open-label study of nivolumab monotherapy (arm A), nivolumab plus ipilimumab combination therapy (arm B) or an investigator's choice chemotherapy (arm C) for the treatment of participants with recurrent or metastatic dMMR/MSI-H CRC. In protocol revision 04, the study expanded with additional participants in 1L setting.

Therefore, the study enrollment includes 2 sequential parts. Part 1 enrollment is open to participants across all lines of therapy, and Part 2 enrollment open only to participants who have not received prior therapy for metastatic disease (1L). Part 2 enrollment starts immediately after completion of part 1 enrollment.

After confirmation of eligibility criteria participants will be randomized to arms A, B or C in a 2:2:1 ratio. Randomization to arm C will be restricted to participants who have received no more than 1 prior line of systemic therapy (0 or 1 line). Part 1 enrollment continues to allow randomization of approximately 442 participants across lines of therapy with centrally confirmed dMMR/MSI-H mCRC as per protocol revision 03.

Approximately 230 additional participants who have not received prior therapy for metastatic disease (1L) with centrally confirmed dMMR/MSI-H mCRC will be randomized during part 2 enrollment.

A continuous evaluation of the discordance rate between local and central testing during the study conduct suggests that approximately 15% of the samples have discordant dMMR/MSI-H results. The observed discordance rate is higher than the initially assumed rate of 10% used for sample size calculation for randomization per local testing. Additionally, poor tissue quality led to the absence of valid central test results in some instances; ie, no confirmation of dMMR/MSI-H status by either central test. Therefore, while the projected number of randomized participants per central testing have not changed, the number of participants per local testing is revised to reflect higher than initially assumed discordance rate.

Part 1 enrollment was completed as of Revised Protocol 06. Part 2 randomization was completed in Apr-2023.

Stratification factors

CA2098HW study participants will be stratified by tumor location (right vs left) and by the number of prior treatments for metastatic disease (none, one, two or more). Stratification by tumor sidedness will continue during Part 2 enrollment, however stratification by line of therapy will not be applicable since enrollment will be open only for participants who have not received prior therapy. Study specific definition of tumor sidedness and line of therapy (number of prior systemic treatments for metastatic disease) are provided in the Appendices 12 and 10, respectively.

Participants will receive treatment until progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration. Study participants from all three arms that discontinue study treatment will enter the Follow Up phase (first treatment Follow Up) and will follow the assessment schedules outlined in Table 2-5.

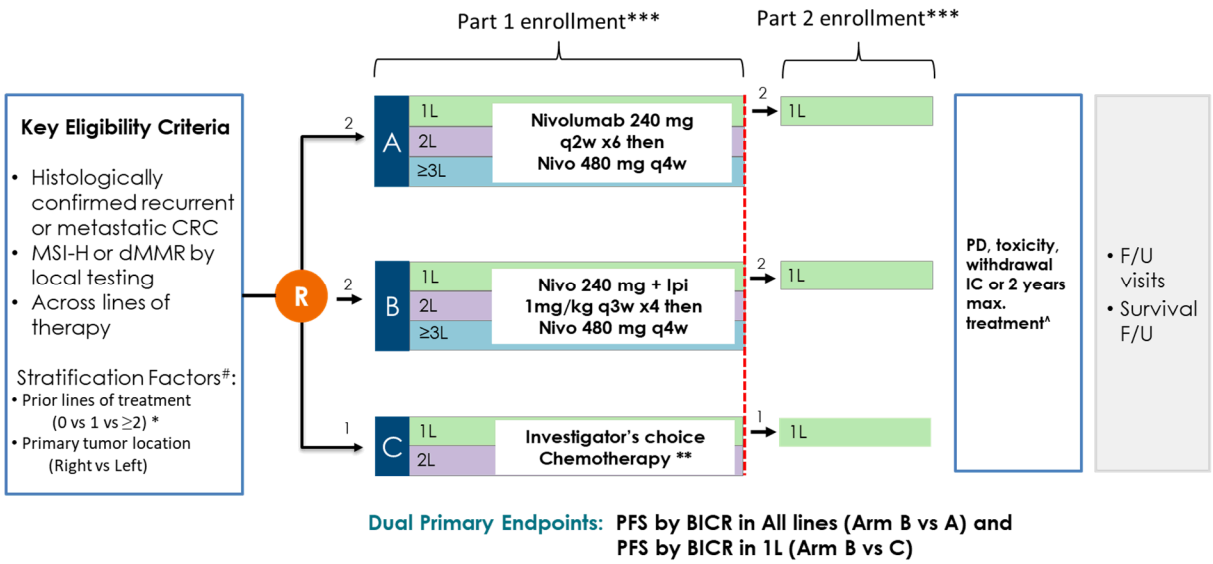
Crossover Cohort

Participants assigned to arm C that experience documented progression of disease (PD) per RECIST 1.1 by Blinded Independent Central Review (BICR) will have an option to crossover to nivolumab plus ipilimumab therapy (Crossover Cohort) provided that they complete at least Follow Up Visit 1 (Table 2-5) within the Follow Up phase and meet all other crossover criteria outlined in the protocol Section 6.3. Crossover Cohort participants will receive treatment until

progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration. After study treatment discontinuation, they will also enter the Follow Up phase (second treatment Follow Up) and will follow the assessment schedules outlined in Table 2-5. The Crossover Cohort starts when participants begins nivolumab plus ipilimumab combination therapy.

The study design schematic and study conduct scheme are presented in Figure 5.1-1 and Figure 5.1-2.

Figure 5.1-1: Study Design Schematic



1L, 2L, ≥3L – subgroups of participants within each study arm for whom study treatment is a 1st line (0 prior lines of systemic therapy), 2nd line (1 prior line of systemic therapy) or 3rd line and beyond (2 or more prior lines of systemic therapy), respectively.

Line of therapy is not a stratification factor during Part 2 enrollment.

* Participants with ≥2 prior lines are randomized only to arm A or B during Part 1 enrollment; only participants with 0 prior lines are randomized during Part 2 enrollment.

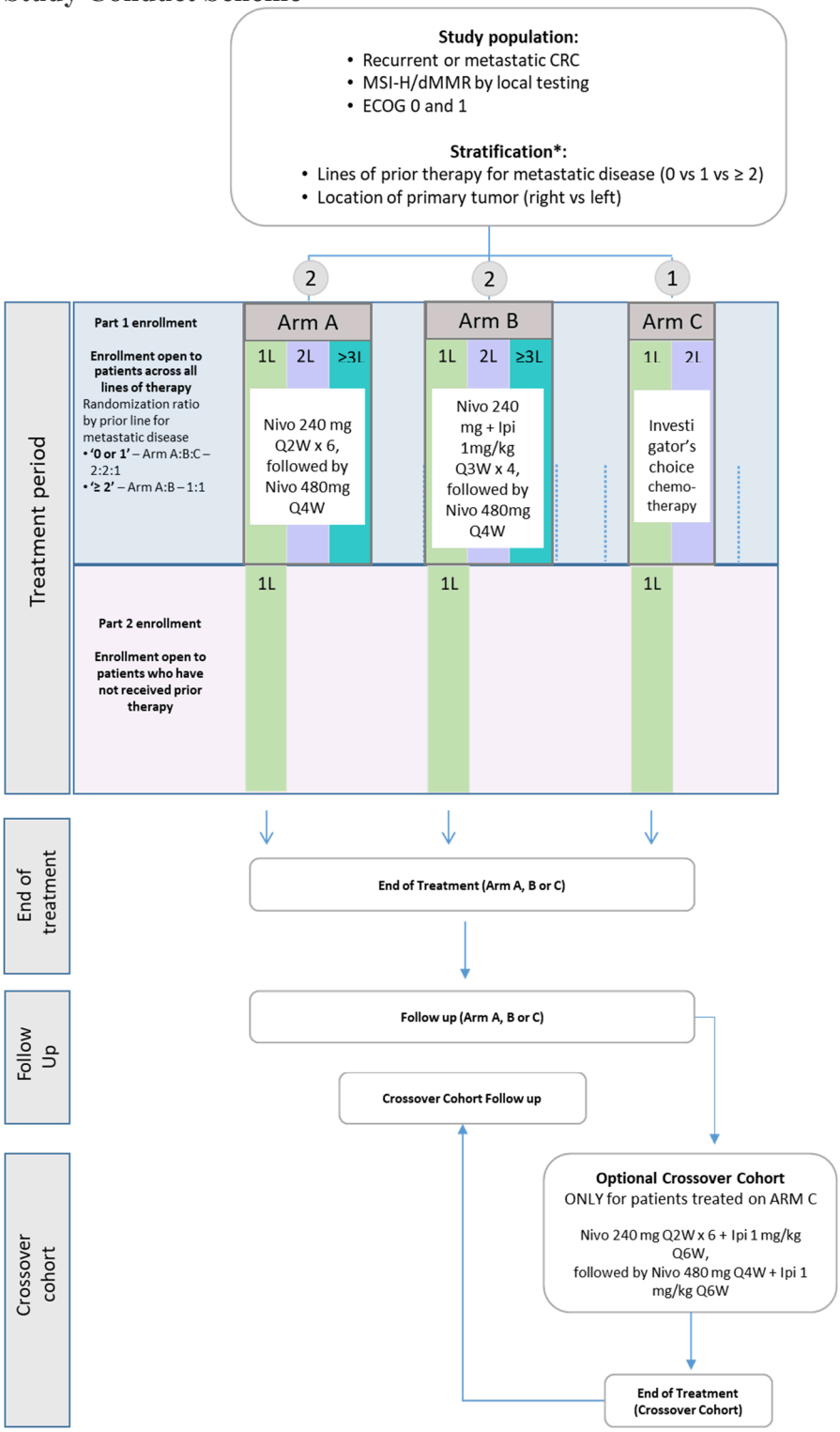
** Optional Crossover for arm C with Nivo + Ipi q6w dosing.

*** Part 1 enrollment continues to allow randomization of approximately 560 participants across lines of therapy with locally confirmed dMMR/MSI-H mCRC. Part 2 enrollment continues to allow randomization of approximately 271 additional participants with locally confirmed dMMR/MSI-H status who have not received prior therapy for metastatic disease (1L). Part 2 randomization was completed in Apr-2023.

^ max treatment duration is not applicable for arm C participants.

Abbreviations BICR, Blinded Independent Central Review; CRC, colorectal cancer; IC, informed consent, MSI-H, microsatellite instability high; dMMR, deficient mismatch repair; PD, progressive disease; PFS, progression free survival.

Figure 5.1-2: Study Conduct Scheme



* Line of therapy is not a stratification factor in Part 2 enrollment

Abbreviations: CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group IC, informed consent, MSI-H, microsatellite instability high; dMMR, deficient mismatch repair

China Sub-study

A China extension will be added to allow continued enrollment of participants from China after the completion of the enrollment to the global study. All details regarding the study design, sample size, and duration of enrollment will be specified in the China-specific protocol.

5.1.1 Data Monitoring Committee and Other External Committees

5.1.1.1 Data Monitoring Committee

A data monitoring committee (DMC) will be utilized to provide an independent evaluation of the study interim data. The DMC charter will describe additional details of the DMC responsibilities and procedures related to the committee operations. The Sponsor will have responsibility for the overall conduct of the study, including managing the communication of study data.

5.1.1.2 Blinded Independent Central Review (BICR)

A BICR will be utilized in this study for determination of BICR-assessed endpoints. Details of BICR procedures will be specified in the BICR Charter. Images will be submitted to an imaging third-party vendor for central review. Sites will be trained prior to enrolling the first study patient. Imaging acquisition guidelines and submission process will be outlined in the Study Imaging Manual to be provided by the vendors. Refer to Section 9.1.1 Imaging Assessment for the Study for further details.

5.2 Number of Participants

It is expected that approximately 831 participants with dMMR/MSI-H mCRC determined by local testing will be randomized to study, including approximately 560 and 271 during part 1 and part 2 enrollment, respectively. These corresponds to randomization of approximately 442 participants across lines of therapy and 230 participants who have not received prior treatment with centrally confirmed dMMR/MSI-H status during part 1 and part 2 enrollment, respectively. These estimations are based on the number of participants with centrally confirmed dMMR/MSI-H status required for evaluation of each primary endpoint and on assumption of discordance rate between local and central testing of 15%.[50]

The study may randomize participants beyond these numbers if 1) discordance rate between local and central dMMR/MSI-H testing exceeds 15% or no central confirmation of dMMR/MSI-H status is available, 2) distribution across lines of therapy significantly deviates from preliminary estimations or 3) increasing number of participants will undergo surgical resection prior to progression event (ie, 15% or more).

5.3 End of Study Definition

The start of the trial is defined as first patient first visit. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

Both nivolumab monotherapy and nivolumab in combination with ipilimumab have shown highly promising activity and durable responses in the treatment of dMMR/MSI-H mCRC beyond first-line.

There is growing body of evidence that immunotherapy is effective not only in the refractory settings but also in earlier lines of treatment. Recently presented data from a randomized phase 3 study comparing pembrolizumab with standard chemotherapy in front-line setting (Keynote-177 study) confirmed superior antitumor activity as reflected by PFS and ORR achieved by anti-PD1 single agent vs chemotherapy in MSI-H mCRC patients.[1]

Indirect comparisons suggest that nivolumab (3 mg/kg) + low-dose ipilimumab (1 mg/kg) combination therapy provides improved clinical benefit versus nivolumab monotherapy with a favorable benefit-risk profile for previously treated patients with dMMR/MSI-H mCRC (≥ 1 prior therapy). Extrapolation of the data from the Keynote-177 study extends these assumptions of improved PFS and OS of IO-IO combination vs IO monotherapy to 1L setting. Accumulating external and internal data in MSI-H mCRC suggest consistent treatment effect in terms of PFS improvement with combination vs monotherapy regardless of the line of therapy justifying study statistical design. Therefore, the randomized design was chosen to confirm the findings of the indirect comparison within the non-randomized study (CA209142) demonstrating superior response rates, improved PFS and OS with nivolumab plus ipilimumab combination therapy compared with nivolumab monotherapy. Moreover, the randomized design will enable more reliable analyses across combination and monotherapy arms between patient and tumor characteristics and disease outcomes, from both efficacy and safety perspectives.

Up to now, no study has reported results on comparative efficacy of dual I-O combination (anti-CTL-4 + anti-PD1) vs chemotherapy in dMMR/MSI-H mCRC patients, including those who have not received prior therapy for metastatic disease or received 1 prior line of therapy. There are 2 (Keynote-177 and COMMIT) ongoing phase 3 clinical studies evaluating efficacy and safety of immunotherapy vs standard of care as 1L therapy in dMMR/MSI-H mCRC patients.[51,52] While the Keynote-177 study compares pembrolizumab single agent with chemotherapy, and the COMMIT study evaluates atezolizumab in combination with chemotherapy vs chemotherapy, no study evaluates the combination of two immunotherapies vs chemotherapy as 1L treatment in dMMR/MSI-H mCRC patients. In the Keynote-177 study, early detriment in terms of PFS was observed with single-agent pembrolizumab compared with chemotherapy leading to the crossing of the PFS curves. These data of IO monotherapy as 1L treatment in MSI-H mCRC patient raises the question if IO-IO combination is able to overcome or reduce the detriment.

To address these questions the study design expands enrollment for participants who have not received prior therapy for metastatic disease.

5.4.1 Rationale for Treatment Setting

The goal of treatment is palliative for the majority of patients with mCRC, while a small subset may achieve cure (liver and/or lung-limited oligometastatic disease). With modern treatment

approaches, median survival can exceed two years for patients who are able to tolerate intensive therapy.[53] Standard of care for initial therapy for mCRC is combination of cytotoxic chemotherapy with biologic agent (anti-VEGF or anti-EGFR). The addition of a biologic agent (anti-VEGF or anti-EGFR) to standard chemotherapy has been shown to improve PFS and OS. Combinations of chemotherapy (FOLFOX or FOLFIRI) and a biologic agent in the first-line setting achieve response rates >40%, and mPFS up to 9-11 months, but toxicities reported such as Grade 3-4 neutropenia or diarrhea can exceed 40%.[54] Furthermore, with aging populations across the globe, some patients with mCRC may not be candidates for such intensive therapy. Confirming efficacy of checkpoint inhibition and IO-IO combination in earlier lines of treatment for dMMR/MSI-H mCRC can allow more patients to benefit from durable response with potentially less persistent toxicity. It should be noted that nivolumab monotherapy and nivolumab plus ipilimumab combination are listed in the NCCN guidelines among treatment options in first-line and beyond for patients who are not appropriate for intensive therapy (category 2B for first line), and for all patients with dMMR/MSI-H mCRC beyond first-line (category 2A).[33]

Immune responses to combination therapy with nivolumab and ipilimumab may be more robust in patients who are chemotherapy-naive.[55] In dMMR/MSI-H mCRC, long term follow up of the monotherapy cohort demonstrated stronger response among patients who had ≤ 2 standard chemotherapies as compared with those who received all three chemotherapies prior to nivolumab.[31] These observations, taken together with the decreased benefit from cytotoxic chemotherapy in the dMMR/MSI-H mCRC population,[16] suggest that a rational approach would be to offer combined immunotherapy to dMMR/MSI-H patients earlier in the course of their disease.

The efficacy and safety of immune check-point inhibitors across all lines of treatment for dMMR/MSI-H mCRC are currently under investigation in clinical trials. The preliminary data from the treatment-naive cohort (C3 Cohort) in the CA209142 study suggest that nivolumab combined with ipilimumab is an active and promising treatment in first-line setting.[56] Moreover, ongoing studies in first-line dMMR/MSI-H mCRC include pembrolizumab monotherapy vs chemotherapy (NCT02563002). The nivolumab monotherapy and combination of nivolumab plus ipilimumab provided higher and more durable response compared to historical control in the non-randomized CA209142 study.[29,31] Therefore, extension of the inclusion criteria allowing the randomization of patient irrespective of prior treatment history to nivolumab monotherapy versus nivolumab and ipilimumab combination provides promisingly effective treatment options even for first-line treatment with manageable safety profile to patients whose tumors may not respond to chemotherapy to the same extent as MSS tumors.

Front-line chemotherapy in unselected mCRC patients is effective as reflected by high rates of ORR (40-60%), mPFS (10-11 months) and mOS (20-30 months).[48] The second-line treatment has lower efficacy compared to first-line therapy. The reported rates of ORR in second-line setting vary significantly from 5 to 20%, with mPFS and mOS reaching approximately 6 months and 11 months, respectively.[57] Retrospective analyses of several studies suggest that patients with

dMMR/MSI-H mCRC may not benefit from chemotherapy to the same extent as patients with MSS tumors. These observations have been recently confirmed by the Keynote-177 study results. The mPFS for front-line chemotherapy arm was 8.2 months, and 33.1% of participants achieved response, including 3.9% complete response.

Availability of such data for front and second-line would allow to optimize dMMR/MSI-H patients' management considering the excellent results from CA209142 study in 1L and chemo-refractory settings.

5.4.2 Rationale for Investigator's Choice Treatment and PFS assumptions in Chemotherapy Arm

Chemotherapy is the only approved treatment option for unselected, including dMMR/MSI-H, mCRC patients who have not received any prior systemic therapy or who have received one prior line of therapy. Since the best way to combine and sequence chemotherapeutic agents is still not established the approach for initial and subsequent treatments may vary in terms of choice of regimen and inclusion of targeted agents.[33,58] Considering that CA2098HW is a global study the investigator's choice standard chemotherapy will include one of 6 SOC regimens (FOLFOX, FOLFIRI with or without Bevacizumab or Cetuximab) recommended by guidelines for initial or subsequent mCRC treatment.

Efficacy results of chemotherapy in front- and second line settings are summarized in the Section 5.4.1. Patients who are refractory to chemotherapy can be treated with regorafenib or TAS-102. Both agents provide modest improvement in mOS vs best supportive care (6.4 versus 5 months for regorafenib; and 9 versus 6.6 months for TAS-102) at the expense of significant adverse events profile.[59] On the other hand nivolumab and nivolumab plus ipilimumab that are approved in this setting provide robust and durable clinical benefit as reflected by significant improvement of PFS and OS in patients with dMMR/MSI-H mCRC.[2,3] Therefore only patients without prior systemic treatment (1L) or those who have had received one prior line of systemic therapy (2L) will be randomized to chemotherapy arm.

The median PFS in unselected patient population with mCRC treated with 1L doublet chemotherapy is approximately 10 months. Reported mPFS in studies with 2L chemotherapy is approximately 6-7 months. Taking into account data from post-hoc analyses of randomized studies and real-world cohorts suggesting shorter mPFS in patients with dMMR/MSI-H mCRC compared to patients with MSS tumors (See Sections 3.2.3 and 5.4.1 for additional details), the mPFS in patients with dMMR/MSI-H mCRC who have not received prior systemic therapy (1L) assumed 9 months, and in patients who have received one prior line of systemic therapy (2L) assumed 5 months. The mPFS assumptions for 1L chemotherapy has been recently confirmed by the Keynote-177 study that reported mPFS of 8.2 months in previously untreated patients who received investigators choice chemotherapy.[1] During part 1 enrollment, approximately equal distribution of 1L and 2L patients in the arm C (this ratio is derived from internal sites feasibility assessment) is projected.

5.4.3 Rationale for Nivolumab Monotherapy

Nivolumab monotherapy provides clinically meaningful and durable responses in dMMR/MSI-H biomarker-selected population beyond second-line, which seem to exceed historical response rates remarkably with standard options. In CA209142 study after median follow up of 21 months of patients treated with nivolumab monotherapy (n = 74), the median DOR per BICR was not reached and the mPFS was 6.6 month (95% CI: 3.0, NE). Landmark PFS rates were 44% (95% CI: 32.6, 55.3) at both 12 and 18 months. Median OS was not reached (95% CI: 19.6, NE), and the OS rates at 12 and 18 months were 72% (95% CI: 60.0-80.9) and 67% (95% CI: 54.9-76.9), respectively.[60] These findings in this pretreated population (beyond first-line) demonstrate the durability of clinical benefit in some patients and justify further study of nivolumab monotherapy in dMMR/MSI-H mCRC patients, including first line.

5.4.4 Rationale for Nivolumab and Ipilimumab Combination

The combination of nivolumab and ipilimumab was chosen based on preclinical and preliminary clinical evidence suggesting synergy between nivolumab and ipilimumab across different tumor types. Nivolumab in combination with ipilimumab, has demonstrated remarkable benefit for several solid tumor types, including previously treated dMMR/MSI-H mCRC.[61] Preliminary evidence from nivolumab plus ipilimumab cohort (n = 119) of CA209142 study demonstrated additional clinical improvement of this combination in mCRC patients over the cohort of patients treated with nivolumab monotherapy (n = 74) beyond second-line of treatment. At data cutoff of Jul 2017 the median follow up in the nivolumab plus ipilimumab combination therapy cohort was 13.4 months (range 9 - 25 months). The BICR-assessed ORR achieved in 49% (95% CI: 39.5, 58.1), including 4% of patients who demonstrated CR. This was numerically higher than in the cohort of 74 patients who received nivolumab monotherapy (31.1%, 95% CI: 20.8, 42.9) in the same study with similar median follow up of 13.4 months.[29] Thus, nivolumab plus ipilimumab combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period. Superior OR rates with nivolumab plus ipilimumab combination were translated to the numerically improved PFS and OS rates over nivolumab monotherapy. The investigator assessed 12-month PFS and OS rates in nivolumab monotherapy and nivolumab plus ipilimumab cohorts were 50% (95% CI: 38-61) vs 71% (95% CI: 61.4, 78.7) and 73% (95% CI: 62-82) vs 85% (95% CI: 77.0-90.2), respectively. In the combination cohort Grade 3 to 4 treatment-related AEs occurred in 32% of patients and were manageable.[62]

Internal data from recent DBL of the CA209142 study as well as external evidence from the Keynote-177 study indicate flattened tails of PFS curves for nivolumab monotherapy and nivolumab plus ipilimumab combination therapies, constant HR for PFS between nivolumab plus ipilimumab combination and nivolumab monotherapy by line of therapy, and stronger than initially anticipated treatment effect of combination vs monotherapy.

5.4.5 Rationale for Optional Crossover from Chemotherapy Arm

Immunotherapy has proven benefit in dMMR/MSI-H mCRC patients and lead to dramatic improvement in PFS and OS in chemo-refractory setting. Nivolumab and nivolumab plus ipilimumab

combination approved in few countries for the treatment of dMMR/MSI-H mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Thus, to ensure access to immunotherapy, across all participating countries to patients that were randomized to arm C and progressed on or after receiving chemotherapy, an optional crossover to nivolumab plus ipilimumab combination therapy is introduced. Eligible patients may receive nivolumab plus ipilimumab combination for a maximum treatment period of 2 years. It is recognized that this crossover immunotherapy treatment may confound any OS endpoints, but it will not affect other key endpoints.

5.4.6 Rationale for Choice of Primary Endpoints

The primary endpoints of the study are PFS per BICR. Although OS is considered the most reliable cancer endpoint, PFS has been an acceptable endpoint to support regulatory approvals in mCRC. PFS has been selected as a primary endpoint for comparison of clinical benefit between nivolumab monotherapy (arm A) and nivolumab plus ipilimumab combination therapy (arm B). Decision to use PFS as a primary endpoint is driven by long OS reported for nivolumab and nivolumab plus ipilimumab in dMMR/MSI-H mCRC in CA209142 study. Demonstration of benefit in terms of OS would require a larger study and/or longer follow up that could be challenging to achieve within clinical study for dMMR/MSI-H mCRC patients. In addition, nonuniform access to subsequent cancer therapy may potentially confound survival analysis. PFS is viewed as benefit on its own right considering the duration of PFS observed with nivolumab alone or in combination with ipilimumab.

Prioritization of PFS over OS for the second primary endpoint is imposed by the optional crossover for patients treated with chemotherapy. Provision of nivolumab plus ipilimumab for patients progressing on chemotherapy will confound OS. The benefit in OS for arm C patients is expected to be substantial after switching to nivolumab plus ipilimumab. Thus, selection of OS as a second primary endpoint, will face the same challenges as comparison of survival between arms A and B. Therefore, PFS being an important indicator of clinical benefit in mCRC, is more suitable as the primary endpoint for CA2098HW trial.

5.4.7 Clinical Validation of Companion Diagnostics

The design of CA209-8HW study accounts for the development of companion diagnostics for dMMR/MSI-H testing (IHC and a PCR-based assays), a post marketing commitment to US FDA. Choice of primary population in CA209-8HW trial consisting of patients with centrally confirmed dMMR/MSI-H mCRC is driven by this companion diagnostic development. Patients' enrollment is based on local testing result allowing rapid accrual and minimizing delay in treatment initiation, while pre-defining primary population (confirmed dMMR/MSI-H by central laboratory) allows adequate clinical validation of the assays. All enrolled patients will have tumor tissue samples analyzed retrospectively in a central laboratory setting, using both the IHC assay and the PCR assay.

5.4.8 Rationale for Tissue Requirements

One of the objectives of the CA2098HW clinical trial is to fulfil the commitment to support the availability of companion in vitro diagnostic device. Therefore, an appropriate analytical and clinical validation study using CA2098HW clinical trial data will be conducted to support labeling

of an immunohistochemistry-and nucleic acid-based in vitro diagnostic devices that are essential to the safe and effective use of nivolumab for patients with tumors that are mismatch repair deficient. To meet this commitment the CA2098HW clinical trial has tissue requirements that are outlined in the inclusion criteria 2 e) (see Section 6.1).

5.4.9 Rationale for Duration of Study Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months,[47,63,64,65, 66] and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[67] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[68]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the 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 participants 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]

Keynote-006 was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of

treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[72]

Recent analysis of the data from CA209142 study in patients with dMMR/MSI-H mCRC tumors suggests that minority of the patients experience relatively late objective response to nivolumab monotherapy (up to Month 23) or nivolumab plus ipilimumab combination (up to Month 14).[73] It is not known yet if treatment discontinuation after 2 years in participants with late partial response impacts on duration of response. Therefore to minimize the potential risk of disease recurrence as a result of premature treatment discontinuation, all patients who achieved objective response within second year of treatment, will continue to receive study therapy for additional 12 months. Thus the proposed approach for treatment duration will not only mitigate the potential risk of disease recurrence in patients with late partial response, but also ensures that patients with objective response to be followed for at least 12 months from the onset of response.

The optimal treatment duration of initial chemotherapy for unresectable disease is controversial. Per NCCN and ESMO guidelines chemotherapy should be administered until disease progression or unacceptable toxicity with potential to switching from initial intensive therapy to less intensive therapy (maintenance therapy) in patients with good response to initial treatment.[33,74]

5.5 Justification for Dose

Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, SCLC, RCC, cHL, SCCHN, UC, and dMMR/MSI-H mCRC using a regimen of either nivolumab 240 mg Q2W or nivolumab 480 mg Q4W.

The nivolumab dose of 240 mg Q2W and 480 mg Q4W were selected based on clinical data and modeling and simulation approaches using 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.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than proportionally with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC participants has recently been updated, using data from 1544 participants from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg participant, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W and 480 mg Q4W in CRC patients from CA209142, a PPK model was used to simulate nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W. Table 5.5-1 presents the comparison of nivolumab exposures at the different dosing regimens in mCRC patients. The geometric mean of all 8 of the key summary measures of nivolumab exposures achieved with 240 mg Q2W dosing were slightly greater (< 10%) relative to the corresponding exposures achieved with 3 mg/kg Q2W. Additionally, the geometric means of nivolumab exposure in the dMMR/MSI-

H mCRC population were greater with 480 mg Q4W dosing relative to 3 mg/kg Q2W dosing for 6 of the 8 summary measures of exposure, namely: Cavg1, Cmax1, Cmin1, Cavgd28, Cavgss and Cmaxss; whereas the exposures were lower by ~19% for Cmind28 and ~11% Cminss. This magnitude of difference is not expected to be clinically significant. Notably, nivolumab concentrations averaged over the first 4-weeks were higher with 480 mg/kg Q4W relative to 3 mg/kg, and approximately twice as high during the first 2 weeks. Therefore, since exposures following 480 mg Q4W are predicted to be similar to those at 3 mg/kg, no impact on efficacy is expected. The PPK model predicted Cmax1 with 480 mg Q4W to be about 117% higher than seen with 3 mg/kg Q2W for dMMR/MSI-H mCRC and this difference is reduced to 46.7% when steady state is achieved. The Cmax achieved with 480 mg Q4W is well below the Cmax achieved by a dose of 10 mg/kg Q2W (Figure 5.5-1), which is a regimen that has been shown to be safe and tolerable. Therefore, no impact on safety is expected with the dosing regimen to be used in this study.

Table 5.5-1: Geometric Mean Exposure for Nivolumab 3 mg/kg Q2W, 240 mg Q2W or 480 mg Q4W, dMMR/MSI-H mCRC

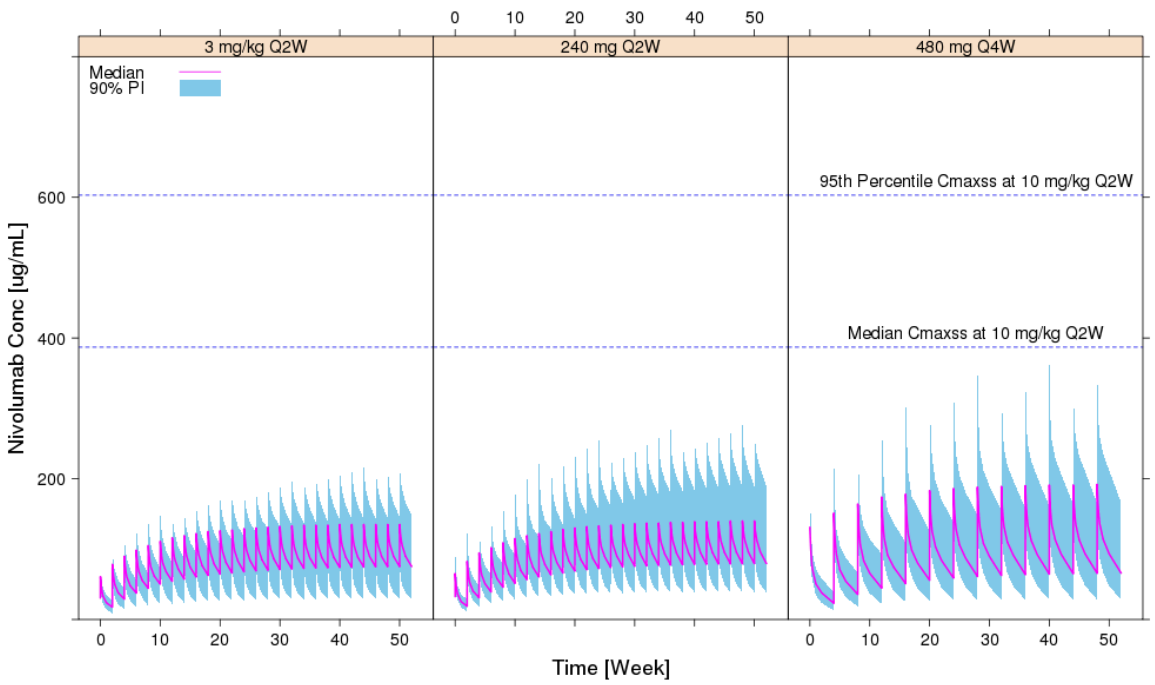
Tumor Type	Summary Exposure	G1 - Nivo 3 mg/kg Q2W GM [µg/mL] (%CV)	G2 - Nivo 240 mg Q2W GM [µg/mL] (%CV)	G3 - Nivo 480 mg Q4W GM [µg/mL] (%CV)	%Diff GM (240 mg) G2-G1[a]	%Diff GM (480 mg) G3-G1[b]
dMMR/MSI-H mCRC (N=62)	CAVG1	26.9(21.8)	29.2(23.5)	43.9(26.5)	8.55	63.2
	CAVGD28	33.8(23.2)	36.6(25.2)	43.9(26.5)	8.28	29.9
	CAVGSS	93.6(41.5)	101(48)	101(48)	7.91	7.91
	CMAX1	60.3(15.3)	65.4(27.9)	131(28)	8.46	117
	CMAXSS	137(32.6)	148(40.9)	201(36.8)	8.03	46.7
	CMIN1	17(27.8)	18.5(29.8)	22.5(36.9)	8.82	32.4
	CMIND28	27.8(29.2)	30.2(32.2)	22.5(36.9)	8.63	-19.1
	CMINSS	73.9(48.3)	80.1(55.5)	65.5(62.3)	8.39	-11.4

[a] Geometric mean (GM) difference in percentage of 240 mg Q2W (G2) relative to 3 mg/kg Q2W (G1)

[b] Geometric mean (GM) difference in percentage of 480 mg Q4W (G3) relative to 3 mg/kg Q2W (G1)

Source: Table 5.1-1 in the DCN 930127488

Figure 5.5-1: Predicted Nivolumab Concentration (with 90% PI) versus Time by Dosing Regimen in Participants with dMMR/MSI-H mCRC



Source: Figure 5.1-5 in DCN 930127488

Note: Median and 95th percentile Cmaxss lines are calculated from 157 participants receiving 10 mg/kg Q2W nivolumab from Studies MDX1106-01, MDX1106-03, and CA209005

In a previous analysis in participants with solid tumors such as NSCLC, RCC, and advanced melanoma treated over a wide dose range, it was determined that the exposure-response relationships were flat for efficacy and safety. In NSCLC participants, Cmin1 was not a significant predictor of efficacy (OR), and the risk of Grade 3+ DR-AE and AE leading to DC/D did not increase with Cavgss. In advanced melanoma participants, nivolumab Cavgss was not a significant predictor of OS; and risk of Grade 3+ DR-AEs and AEs leading to DC/D in advanced melanoma participants did not increase with higher exposures. In advanced RCC participants, Cavgss was not a significant predictor of hazard of death and the risk of AE-DC/D actually decreased with increasing Cavgss. Given that the E-R relationships in dMMR/MSI-H mCRC are expected to be similar to what has been previously observed, and that the exposures with 240 mg Q2W and 480 mg Q4W are expected to be on the flat portion of the E-R curve, the PPK data presented support the use of 240 mg Q2W and 480 mg Q4W in these participants.

Based on the collective understanding of nivolumab PK, flat exposure-response relationships for safety and efficacy previously observed, and the well-established safety up to the 10 mg/kg Q2W dose level, the benefit-risk profiles following nivolumab 240 mg Q2W and 480 mg Q4W are expected to be similar to that following nivolumab 3 mg/kg Q2W for participants with dMMR/MSI-H mCRC.

Thus nivolumab 240 mg over 30 minutes will be used across both arms (nivolumab monotherapy and nivolumab plus ipilimumab combination) for the first 12 weeks, and nivolumab 480 mg will be used thereafter.

Rationale for nivolumab/ipilimumab combination schedule

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 in line with the approved schedule for ipilimumab which is every 3 weeks for a total of four doses in the FDA and EMA approved label dosing section, ipilimumab will be administered every 3 weeks for a total of 4 doses. Additionally, data on the clinical efficacy of the combination therapy of 3 mg/kg nivolumab + 1 mg/kg ipilimumab in the dMMR/MSI-H CRC population (CA209142 combo CSR) is described in Section 3.2.3.

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.[75] 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.[76] 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 the Crossover Cohort with the expectation that there will not be changes in the safety profile, as has been demonstrated in NSCLC and in CA209142 study

for the cohort of dMMR/MSI-H mCRC patients who have not received prior systemic therapy for metastatic disease. Nivolumab (3 mg/kg Q2W) plus ipilimumab (1 mg/kg Q6W) combination was studied in dMMR/MSI-H mCRC patients in front-line setting (C3 cohort in CA209142 study).[77] This combination demonstrated robust and durable clinical benefit as a 1L treatment for dMMR/MSI-H mCRC. The ORR and disease control rate (DCR) were 60% and 84%, respectively, with a 7% complete response rate. Median DOR was not reached. At 12 months, PFS and OS rates were 77% and 83%, respectively. Importantly, the safety profile was comparable to Nivolumab monotherapy. The Grade 3 to 4 treatment related AEs (TRAEs) observed in 16% of patients, and the rate of discontinuation due to TRAEs was low (7%).

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants or their legally authorized representative (see Appendix 2) must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Histologically confirmed recurrent or metastatic CRC irrespective of prior treatment history with chemotherapy and/or targeted agents not amenable to surgery. **Inclusion Criterion 2a is applicable only during Part 1 enrollment of the study.**

b) Known tumor MSI-H or dMMR status per local standard of practice. See Appendix 8.

c) All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria. See Appendix 7.

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

e) Adequate tumor tissue available. Tumor tissue specimens, either a FFPE tissue block (preferred) or unstained tumor tissue sections (minimum of 30 positively charged slides) from primary or metastatic site, must be submitted to the central laboratory. Central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Tumor tissue specimen must meet either of the criteria below:

i) Obtained within 3 months of enrollment with no intervening systemic anti-cancer treatment between time of acquisition and randomization AND this must be the same tissue sample as was used for local MMR/MSI testing.

OR

ii) If above is not available, archival tissue can be accepted if the same tissue was used for MMR/MSI testing.

Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone samples are also unacceptable for submission.

f) ECOG Performance Status ≤ 1 (see Appendix 6)

g) Histologically confirmed recurrent or metastatic CRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery. Participants treated with adjuvant chemotherapy are eligible if disease progression occurred later than 6 months (≥ 6 months) after completion of chemotherapy. **Inclusion Criterion 2g is applicable during Part 2 enrollment of the study**

3) Age and Reproductive Status

a) Males and Females, ages 18 years and above

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) receiving nivolumab without or with ipilimumab must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus at least 5 months after the last dose of study treatment (ie, the time required for nivolumab to undergo approximately five half-lives). Women of childbearing potential (WOCBP) receiving investigator's choice chemotherapy must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus at least 6 months after the last dose of study treatment.

e) Males who are sexually active with WOCBP and who are assigned to receive nivolumab without or with ipilimumab are exempt from contraceptive requirements. Males who are sexually active with WOCBP and who are assigned to receive chemotherapy must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) plus at least 6 months after the last dose of study treatment. In addition, male participants assigned to chemotherapy arm must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in Section 2.

Investigators shall counsel WOCBP (as defined in Appendix 4) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, and the implications of an unexpected pregnancy. Additionally, male participants assigned to

chemotherapy arm should be counseled about the potential of fetal toxicity occurring due to transmission of study intervention present in seminal fluid to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is already pregnant. WOCBP participants and WOCBP who are sexual partners of male participants are required to use a highly effective method of contraception (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. (CT scan is acceptable if there is a contraindication for MRI). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 14 days prior to study drug administration.

b) Ascites that cannot be controlled with medical therapy alone. **Exclusion Criterion 1b is no longer applicable per Protocol revision 04**.

2) Medical Conditions

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

b) History of interstitial lung disease or pneumonitis.

c) Known history of positive test for HIV or known AIDS. NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 9).

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

e) Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured (for example squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast).

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

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

o) Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency. Systematic screening for DPD deficiency has to be performed at sites where mandated locally (see Appendix 9)

Additional exclusion criteria (h-n) for participants who have not received prior systemic therapy or who have received one prior line of systemic therapy.

h) Prior major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization. Any wound-related AE(s) must have resolved prior to randomization.

i) Clinically significant cardiovascular disease, including but not limited to congenital long QT syndrome. Pre-existing hypertension should be adequately controlled.

j) Clinically significant bleeding diathesis or coagulopathy.

k) Myocardial infarction, arterial thrombosis or cerebrovascular accident within 6 months prior to enrollment.

l) Non-healing wound, ulcer, or bone fracture.

m) History of gastrointestinal perforation or abscess within 6 month prior to enrollment.

n) Persistence of toxicities related to first-line chemotherapy grade > 1 (CTCAE v5.0) (except alopecia, fatigue or peripheral sensory neuropathy which can be Grade 2)

3) Prior/Concomitant Therapy

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

b) Participants who received cancer-related Investigational Products (IPs) within 28 days or 5 half-lives, whichever is longer, prior to randomization.

c) Prior systemic anti-cancer treatment must have been completed at least 14 days prior to randomization.

d) Prior focal palliative radiotherapy must have been completed at least 14 days prior to randomization.

e) Participants who have received a live/attenuated vaccine within 30 days of randomization (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]). If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized.

f) Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to randomization. Refer to Section 7.7.1 for prohibited therapies.

g) Participants who received treatment in this clinical study (CA2098HW).

Additional exclusion criteria for participants who have not received prior systemic therapy or who have received one prior line of systemic therapy.

h) Current treatment with a non-topical medications known to be a strong inducers or inhibitors of CYP3A4, or strong inhibitors of UGT1A1. However, patients who either discontinue this treatment or switch to another medication at least 7 days prior to starting study treatment are eligible.

4) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100×10^3/μL

d) Hemoglobin < 9.0 g/dL (transfusion to achieve the level of hemoglobin ≥ 9 g/dL is not permitted within 7 days of this laboratory assessment)

e) PT/INR and PTT > 1.5 × ULN unless participants are receiving anticoagulant therapy and their INR is stable and within the recommended range for the desired level of anticoagulation.

f) Serum creatinine > 1.5 × ULN, unless creatinine clearance (CLcr) ≥ 40 mL/minute (measured or calculated using the Cockcroft-Gault formula)

g) AST or ALT > 3.0 × ULN, unless participant has documented liver metastases in which case AST/ALT > 5.0 × ULN are exclusionary

h) Total bilirubin > 1.5 × ULN (except participants with Gilbert syndrome who must have a total bilirubin level of < 3.0 × ULN)

i) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, HBsAg, Australia antigen positive, or hepatitis C antibody (anti-HCV) positive (except if HCV RNA negative)

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

Additional exclusion criteria for participants who have not received prior systemic therapy or who have received one line prior systemic therapy.

k) For participants with proteinuria ≥2+ by urine dipstick or urinalysis at baseline, 24-hr urine must be collected. Proteinuria > 1g/24hrs is exclusionary. It is acceptable to estimate urine protein to creatinine ratio (UPCR) instead of 24hr urine collection. UPCR > 1000 mg/g is exclusionary.

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

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

6.3 Optional Crossover for Participants treated in the Arm C

Participants in arm C who have BICR-confirmed PD on or following Investigator's Choice chemotherapy have the option to receive nivolumab plus ipilimumab combination therapy (see Figure 5.1-2). Crossover is optional and is at the discretion of investigator. **To be eligible to crossover to** nivolumab plus ipilimumab combination therapy the following criteria should be met:

1) BICR-confirmed PD per RECIST 1.1
2) ECOG Performance Status 0 or 1
3) Available tumor tissue sample obtained upon progression on arm C, if medically feasible
4) No exposure to any systemic anticancer therapies after discontinuation of chemotherapy in arm C
5) Completed Follow-up Visit 1 after discontinuation of treatment on arm C (occurs approximately 30 days after the last dose of study treatment)

In addition the investigator must ensure that the participant meets all other eligibility criteria based on inclusion and exclusion criteria of the protocol as described below:

Inclusion criteria (Crossover Cohort ONLY):

1) Signed Written Informed Consent

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

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

2) Age and Reproductive Status

a) Males and Females, ages 18 years and above

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) receiving nivolumab without or with ipilimumab must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus at least 5 months after the last dose of study treatment (i.e., the time required for nivolumab to undergo approximately five half-lives).

e) Males who are sexually active with WOCBP and who are assigned to receive nivolumab without or with ipilimumab are exempt from contraceptive requirements.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in Section 2.

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

Exclusion criteria (Crossover Cohort ONLY):

1) **Target Disease Exceptions**
   a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. (CT scan is acceptable if there is a contraindication for MRI). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 14 days prior to study drug administration.
   b) Ascites that cannot be controlled with medical therapy alone. **Exclusion Criterion 1b is no longer applicable per Protocol revision 04**.
2) **Medical Conditions**
   a) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
   b) History of interstitial lung disease or pneumonitis.
   c) Known history of positive test for HIV or known AIDS. NOTE: Testing for HIV must be performed at sites where mandated locally (see Appendix 9).
   d) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
   e) Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured (squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast).
   f) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
   g) Any other sound medical, psychiatric and/or social reason as determined by the investigator.
3) **Prior/Concomitant Therapy**
   a) Prior focal palliative radiotherapy must have been completed at least 14 days prior to vial assignment.

b) Participants who have received a live/attenuated vaccine within 30 days of vial assignment (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

c) Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to vial assignment. Refer to Section 7.7.1 for prohibited therapies.

4) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100×10^3/μL

d) Hemoglobin < 9.0 g/dL (transfusion to achieve the level of hemoglobin ≥ 9 g/dL is not permitted within 7 days of this laboratory assessment)

e) PT/INR and PTT > 1.5 × ULN unless participants are receiving anticoagulant therapy and their INR is stable and within the recommended range for the desired level of anticoagulation.

f) Serum creatinine > 1.5 × ULN, unless creatinine clearance (CLcr) ≥ 40 mL/minute (measured or calculated using the Cockcroft-Gault formula)

g) AST or ALT > 3.0 × ULN, unless participant has documented liver metastases in which case AST/ALT > 5.0 × ULN are exclusionary

h) Total bilirubin > 1.5 × ULN (except participants with Gilbert syndrome who must have a total bilirubin level of < 3.0 × ULN)

i) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, HBsAg, Australia antigen positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV RNA negative)

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

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

Upon confirmation of eligibility to enter the Crossover Cohort participants will receive nivolumab plus ipilimumab combination therapy for a maximum of 2 years (including treatment beyond progression) or less if treatment to be discontinued due to disease progression, toxicity or other reasons. Participants that complete treatment in the Crossover Cohort will enter the Follow Up phase (second treatment Follow Up) and will follow the assessment schedules outlined in the Table 2-5 of the protocol.

Arm C participants who enter the Follow Up phase (first treatment Follow Up) without PD should follow the assessment schedules per protocol. If they experience PD during Follow Up phase that is confirmed by BICR they should be assessed against eligibility criteria for Crossover Cohort.

Participants who are not eligible to enter the Crossover Cohort will continue to follow the assessment schedules for Follow Up phase of the study per Table 2-5.

6.4 Lifestyle Restrictions

Not applicable. No restrictions are required. Please also refer to local SOC products labels for possible restrictions.

6.5 Screen Failures

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

6.5.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented and assigned a new participant number via IRT.

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

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

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

7 TREATMENT

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

Study treatment includes the following IP/IMPs:

- Nivolumab
- Ipilimumab
- Oxaliplatin
- Leucovorin

- Fluorouracil
- Irinotecan
- Bevacizumab
- Cetuximab

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.

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.

Table 7-1: Study treatments for CA2098HW

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP	Open label	Vial or Various packaging configurations	Refer to the label on container and/or pharmacy manual
Ipilimumab Solution for Injection	200 mg (5 mg/mL) and 50 mg (5 mg/mL)	IP	Open-label	Vial or Various packaging configurations	Refer to the label on container and/or pharmacy manual
Oxaliplatin[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Leucovorin (folinic acid)[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Fluorouracil[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Irinotecan[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Bevacizumab[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.
Cetuximab[a,b]	various strengths	IP	Open label	Vial and various packaging configurations	Refer to the label on container and/or Pharmacy manual.

[a] These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. In these cases, products may be in a different pack size/potency/pharmaceutical form than listed in the table. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics.

[b] Potency, packaging, and storage conditions may vary for China. Storage conditions will be indicated on the label.

7.1 Treatments Administered

7.1.1 Study Treatment Duration

The study treatment will be given until one of the following conditions are met, whichever occurs first:

- Disease progression, unless participant will receive treatment beyond progression. Treatment beyond progression is applicable for participants randomized to arm A, B, or enrolled to Crossover Cohort.
- Unacceptable toxicity
- Withdrawal of consent
- Maximum treatment duration as described below (not applicable for arm C participants)
- The end of study

In this study **maximum treatment duration** for arm A or arm B will be 2 years from the first dose of study treatment EXCEPT in participants with late response (during second year of treatment). In participants with late response study treatment will continue for up to an additional 12 months after onset of response, in absence of disease progression, unacceptable toxicity, withdrawal of consent. Above defined maximum treatment duration includes treatment beyond progression. Participants enrolled to Crossover Cohort may have **maximum treatment duration,** including treatment beyond progression, of 2 years from the first dose in Crossover Cohort.

7.1.2 Treatment Schedules

The selection and timing of dose for each participant is summarized in Table 7.1.2-1 through Table 7.1.2-4. The first dose is to be administered within 3 days following randomization/vial assignment.

Table 7.1.2-1: Selection and Timing of Dose for Nivolumab Monotherapy (Arm A). Cycles 1-2, Cycle 3 and Beyond

	Cycle 1 (cycle = 6 weeks)			Cycle 2 (cycle = 6 weeks)			Cycle 3 and Beyond (cycle = 4 weeks)
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1 of every 4 weeks
Nivolumab, 240 mg flat dose	X	X	X	X	X	X	
Nivolumab, 480 mg flat dose							X

Table 7.1.2-2: Selection and Timing of Dose for Nivolumab plus Ipilimumab Combination Therapy (Arm B). Cycles 1-2, Cycle 3 and Beyond

	Cycle 1 (cycle = 6 weeks)		Cycle 2 (cycle = 6 weeks)		Cycle 3 and Beyond (cycle = 4 weeks)
	Day 1	Day 22	Day 1	Day 22	Day 1 of every 4 weeks
Nivolumab, 240 mg flat dose	X	X	X	X	
Ipilimumab, 1 mg/kg	X	X	X	X	
Nivolumab, 480 mg flat dose					X

Table 7.1.2-3: Selection and Timing of Dose for Chemotherapy (Arm C). Cycles 1-2, Cycle 3 and Beyond

	Cycle 1 (cycle = 6 weeks)			Cycle 2 (cycle = 6 weeks)			Cycle 3 and Beyond (cycle = 4 weeks)	
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15
Bevacizumab, 5 mg/kg	X	X	X	X	X	X	X	X
Cetuximab, 500 mg/m^2	X	X	X	X	X	X	X	X
Oxaliplatin, 85 mg/m^2	X	X	X	X	X	X	X	X
Irinotecan, 180 mg/m^2	X	X	X	X	X	X	X	X
Leucovorin, 400 mg/m^2	X	X	X	X	X	X	X	X
Fluorouracil bolus, 400 mg/m^2	X	X	X	X	X	X	X	X
Fluorouracil infusion, 2400 mg/m^2 over 46 hours	X	X	X	X	X	X	X	X

Table 7.1.2-4: Selection and Timing of Dose for Crossover Cohort. Cycles 1-2, Cycle 3 and Beyond

	Cycle 1 (cycle = 6 weeks)			Cycle 2 (cycle = 6 weeks)			Cycle 3 and Beyond (cycle = 4 weeks)	
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15
Nivolumab, 240 mg flat dose	X	X	X	X	X	X		
Ipilimumab, 1 mg/kg	X			X			X C3D1 and D1 of every 3 cycles	X C4D15 and D15 of every 3 cycles
Nivolumab, 480 mg flat dose							X	

7.1.2.1 Arm A - Nivolumab Monotherapy

Participants should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1, and every 2 weeks (± 3 days) thereafter during Cycles 1 and 2 for a total of 6 doses (Q2W × 6 doses). Starting from Cycle 3 Day 1 participants should receive nivolumab as a 30 minutes infusion at a dose of 480 mg every 4 weeks (Q4W). The infusion start and stop time will be recorded in the CRF. Treatment with nivolumab will continue as defined in Section 7.1.1.

7.1.2.2 Arm B - Nivolumab Plus Ipilimumab (Q3W x 4)

Participants randomized to the nivolumab plus ipilimumab arm should receive nivolumab at a dose of 240 mg as a 30 minute IV infusion followed by ipilimumab at a dose of 1 mg/kg administered IV over 30 minutes on Day 1 of Cycle 1 and every 3 weeks (± 3 days) thereafter during Cycles 1 and 2 for a total of 4 doses (Q3W × 4 doses). Starting from Cycle 3 Day 1 participants should receive nivolumab as a 30 minutes infusion at a dose of 480 mg every 4 weeks (Q4W). The infusion start and stop time for nivolumab and ipilimumab will be recorded in the CRF, respectively. Treatment with nivolumab will continue as described in Section 7.1.1. Ipilimumab can be discontinued earlier due to unacceptable toxicity as described in Section 8.1.1. Ipilimumab is not permitted to continue on study after nivolumab is discontinued.

When both nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab and will start after the infusion line has been flushed, filters changed and patient has been observed for approximately 30 minutes to ensure no infusion reaction has occurred. Participants should be carefully monitored for infusion reactions during nivolumab or ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6.

7.1.2.3 Arm C - Investigator's Choice Chemotherapy

Participants randomized to the chemotherapy arm may receive one of 6 SOC regimens described below.

mFOLFOX6

Participants who will receive mFOLFOX6 will receive oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 during Cycles 1 and 2. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.

mFOLFOX6 + bevacizumab

Participants who will receive mFOLFOX6 + bevacizumab regimen, will have bevacizumab administered first, followed by mFOLFOX6.

It is recommended that the first administration (C1D1) of bevacizumab 5 mg/kg to be delivered over a 90-minute infusion. If well tolerated the second administration (C1D15) will delivered over

60 min; if the 60-minute infusion is well tolerated, all subsequent infusions will be delivered over 30 min. Sites may follow local institutional standards for bevacizumab administration.

Bevacizumab 5 mg/kg administration will then be followed by oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles (see Table 7.1.2-3). The infusion start and stop time will be recorded in the CRF.

mFOLFOX6 + cetuximab

Participants who will receive FOLFOX + cetuximab regimen, will have cetuximab administered first, followed by FOLFOX.

It is recommended that the first administration (C1D1) of cetuximab 500 mg/m^2 to be delivered over 2 hours. If well tolerated all subsequent administrations can be delivered over 1 hour. Sites may follow local institutional standards for cetuximab administration.

Cetuximab 500 mg/m^2 administration will then be followed by oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles (see Table 7.1.2-3). The infusion start and stop time will be recorded in the CRF.

FOLFIRI

Participants who will be assigned to receive FOLFIRI will receive irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles. The infusion start and stop time will be recorded in the CRF. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.

FOLFIRI + bevacizumab

Participants who will receive FOLFIRI + bevacizumab regimen, will have bevacizumab administered first, followed by FOLFIRI.

It is recommended that the first administration (C1D1) of bevacizumab 5 mg/kg to be delivered over a 90-minute infusion. If well tolerated the second administration (C1D15) will delivered over 60 min; if the 60-minute infusion is well tolerated, all subsequent infusions will be delivered over 30 min. Sites may follow local institutional standards for bevacizumab administration.

Bevacizumab 5 mg/kg administration will then be followed by irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles (see Table 7.1.2-3). The infusion start and stop time will be recorded in the CRF.

FOLFIRI + cetuximab

Participants who will receive FOLFIRI + cetuximab regimen, will have cetuximab administered first, followed by FOLFIRI.

It's recommended that the first administration (C1D1) of cetuximab 500 mg/m^2 to be delivered over 2 hours. If well tolerated all subsequent administrations can be delivered over 1 hour. Sites may follow local institutional standards for cetuximab administration.

Cetuximab 500 mg/m^2 administration will then be followed by irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles (see Table 7.1.2-3). The infusion start and stop time will be recorded in the CRF.

7.1.2.4 Crossover Cohort - Nivolumab Plus Ipilimumab (Q6W continuously)

Participants who will meet all the criteria to enroll to the optional crossover cohort will receive nivolumab plus ipilimumab therapy. Nivolumab at a dose of 240 mg will be administered as a 30 minute IV infusion on Day 1 of Cycle 1 and every 2 weeks (± 3 days) thereafter during Cycles 1 and 2 for a total of 6 doses (Q2W x 6 doses). Starting from Cycle 3 Day 1 participants should receive nivolumab as a 30 minutes infusion at a dose of 480 mg every 4 weeks (Q4W). The infusion start and stop time for nivolumab and ipilimumab will be recorded in the CRF, respectively. Ipilimumab at a dose of 1 mg/kg will administered IV over 30 minutes on Day 1 of Cycle 1 and every 6 weeks (± 3 days) thereafter (see Table 7.1.2-4).

Treatment with nivolumab and ipilimumab in crossover cohort will continue as described in Section 7.1.1. Ipilimumab can be discontinued earlier due to unacceptable toxicity as described in Section 8.1.1. Ipilimumab is not permitted to continue on study after nivolumab is discontinued.

When both nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab and will start after the infusion line has been flushed, filters changed and patient has been observed for approximately 30 minutes to ensure no infusion reaction has occurred. Participants should be carefully monitored for infusion reactions during nivolumab or ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6.

7.1.3 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of study drugs in arm A, arm B, or Crossover Cohort. See Section 7.4.6 for premedication recommendations following a nivolumab or ipilimumab-related infusion reaction. For participants randomized to arm C premedication may be administrated per local standard.

7.2 Method of Treatment Assignment

CA2098HW is a randomized, open-label study. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by using an IRT to obtain the participant number. Every participant that signs the informed consent form must be assigned a participant number using IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

7.2.1 Initial Treatment Assignment

All participants will be centrally randomized using an IRT. Before the study is initiated, each site user will receive log in information and directions on how to access the IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth
- MSI/MMR Status

Once enrolled in IRT, enrolled participants that have met all eligibility criteria will be ready for randomization and drug vial assignment through the IRT. All tissue submitted for participants will be assessed for quality with an H&E stain, and only those participants who have met tissue quality thresholds can be randomized and assigned study drug. The choice of chemotherapy regimen should be declared prior to randomization and this information be documented in the patients' medical records.

The following information is required for randomization

- Participant number
- Year of birth
- Confirmation that evaluable tumor tissue has been received at the central lab
- Tumor sidedness (right, left)*
- Number of prior treatments for metastatic disease (none, one, two or more)*

*Study specific definitions of the number of prior treatments for metastatic disease (line of therapy) and tumor sidedness are provided in the Appendices 10 and 12, respectively.

Randomization during Part 1 enrollment

Participants meeting all eligibility criteria will be randomized to the study. The randomization ratio across study arms will be defined according to the number of prior lines of systemic treatments for metastatic disease the participant has received. Participants who have not received (1L), or who have received one (2L) prior line of systemic therapy for metastatic disease will be randomized in a 2:2:1 ratio to nivolumab monotherapy, nivolumab plus ipilimumab combination therapy or

chemotherapy arms stratified by tumor sidedness and number of prior treatments for metastatic disease. Participants who have received two or more prior lines of therapy for metastatic disease will be randomized in a 1:1 ratio to receive nivolumab monotherapy or nivolumab plus ipilimumab combination therapy stratified by tumor sidedness and number of prior treatments. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Randomization during Part 2 enrollment

1L participants meeting all eligibility criteria will be randomized in a 2:2:1 ratio to nivolumab monotherapy, nivolumab plus ipilimumab combination therapy or chemotherapy arms stratified by tumor sidedness. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Every effort should be made to avoid randomizing participants who will not be treated. For participants who are randomized but never treated a minimal amount of data must be collected: all baseline data, SAEs. If available information on the off treatment reason and participant status should be collected.

7.2.2 Crossover Cohort Treatment Assignment

Participants in arm C who have BICR-documented PD on or following treatment with investigator's choice chemotherapy have the option to receive nivolumab plus ipilimumab combination therapy (see Figure 5.1-2). Once it has been confirmed that a participant meets all criteria for entry into the Crossover Cohort (Section 6.3), cohort registration and drug assignment will be made using the IRT system. For participants enrolled in the Crossover Cohort, the IVRS will assign the nivolumab plus ipilimumab treatment. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2). The exact procedures for using the IRT and information required for assignment to the Crossover Cohort will be detailed in the IRT manual.

7.3 Blinding

This is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an Interactive Response Technology (IRT). Assessment of primary end point (PFS per BICR) will be done by BICR who will remained blinded to patient treatment assignment.

Designated staff of Bristol-Myers Squibb Research & Development may obtain the randomization codes prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) may obtain the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. BMS will not generate any aggregated reports until pre-specified interim or final analyses. An independent external statistical group will be utilized to conduct unblinded monitoring of pooled events of the two corresponding arms of each comparison in order to track the number of events by each comparison.

7.4 Dosage Modification

Participants will be monitored continuously for AEs while on study therapy. Participants will be instructed to notify their physician for any and all AEs. If AEs are considered to be related to study treatment, every attempt must be made to attribute individual study treatment to adverse event, if possible, or to the combination regimen.

Guidance for Dose Modification for Nivolumab and/or Ipilimumab

Dose modifications for arm A, arm B, and the Crossover Cohort should comply with the protocol Sections 7.4.1.1 (Delay), 7.4.2.1 (Reduction), and 7.4.3.1 (Criteria to Resume Treatment). For the reporting of all AEs, including severity, on case report forms, please follow the definitions in CTCAE version 5 (see Section 9.2 for more details). AE criteria for delaying, resuming, and discontinuing of study treatment is provided in Table 7.4-1.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline
		When administered with ipilimumab: Permanently discontinue Ipilimumab	Nivolumab monotherapy may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab monotherapy, permanently discontinue
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT, or T.bili increased	AST or ALT > 3x and ≤5x ULN or T.bili >1.5x and ≤3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	In most cases of concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, study treatment will be permanently discontinued. However, in patients with baseline elevation of liver enzymes and/or T.bili levels if the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur prior to resuming therapy.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor/ designee needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor/ designee needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/ Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor/ designee needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor/ designee needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area.

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life-threatening, with symptoms at rest or with minimal activity or exertion, and/or where	Permanently discontinue	

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
	intervention indicated.		
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	

Table 7.4-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab Monotherapy (Arm A), Nivolumab Plus Ipilimumab Combination Therapy (Arm B) or Crossover Cohort

Drug-Related AE per CTCAE v5	Severity	Action Taken[a]	Clarifications, Exceptions, and Resume Criteria
Other Lab abnormalities			
Other Drug-Related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: Grade 4 neutropenia ≤ 7 days. Grade 4 lymphopenia or leukopenia. Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.6 on Treatment of Related Infusion Reactions

[a] All actions taken, clarifications, exceptions, and resume criteria apply to nivolumab monotherapy (arm A), nivolumab plus ipilimumab combination therapy (arm B) or crossover cohort.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; GBS = Guillain-Barre syndrome; MG = Myasthenia gravis; SJS = Stevens-Johnson syndrome; T.bili = total bilirubin; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

Guidance for Dose Modification for Chemotherapy

Dose modifications for arm C (chemotherapy) provided in the protocol Sections 7.4.1.2, 7.4.2.2, and 7.4.5 serve as a recommendation. Chemotherapy dose modifications should be applied by the

investigator's judgment and according to local standards. The general guidance for dose modification for chemotherapy are summarized below.

- Treatment for the first cycle should only commence if all eligibility criteria are met and the participant has been randomized. For the first dosing of study treatment all components of the regimen should be administered. For all subsequent dosing, dose delay/modification is permitted per local standards.
- Doses of any study drug omitted for toxicity are not replaced or restored. Supportive care (for example, colony-stimulating factors [CSFs], blood and blood products, etc. can be administered in accordance with the latest American Society of Clinical Oncology (ASCO) or other equivalent guidelines).
- Dose modification, for non-serious and non-life-threatening toxicities like alopecia, altered taste or nail changes may not be required and the final decision is left to the discretion of the treating investigator.
- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest CTCAE grading.
- If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled.

If uracil testing is locally required, and blood uracil level is between ≥16 ng/mL and < 150 ng/mL (evoking partial deficit in DPD), the dose of 5-FU, has to be adapted taking into account the blood uracil level and the other risk factors (dose scheme, participant's age, participant's general condition). A therapeutic adjustment should be performed before next 5-FU dosing depending on treatment tolerability and pharmacologic follow-up if available. It is essential to be particularly vigilant with regard to participants whose blood uracil level is above the upper limit of the normal, especially when this level is high, although less than 150 ng/mL.

7.4.1 Dose Delay Criteria

7.4.1.1 Dose Delay Criteria for Nivolumab and/or Ipilimumab

- Table 7.4-1 provides criteria for nivolumab or nivolumab plus ipilimumab dose delay due to immune mediated AE.

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

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

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

treatment criteria are met. Participants may be dosed no less than 12 days and 19 days from the previous treatment during Q2W (nivolumab) and Q3W (nivolumab combined with ipilimumab) dosing, respectively. During Q4W dosing participants may be dosed no less than 25 days from the previous treatment.

If dose delay is necessary for participants during combination treatment, 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.

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

7.4.1.2 Dose Delay Criteria for Investigator's Choice of Chemotherapy

In arm C, dosing of chemotherapy drugs in the regimen selected as the investigator's choice chemotherapy should be delayed for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For details on dose delay and other dose modifications, and discontinuations due to AEs refer to the protocol Section 7.4.1.2 and 8.1.2.

On C1D1 all components of study treatment should be administered. For all subsequent dosing any individual component of the study treatment can be delayed as per local standards.

7.4.2 Dose Reductions

7.4.2.1 Dose Reduction for Nivolumab and/or Ipilimumab

There will be no dose escalations or reductions of nivolumab allowed. Ipilimumab dosing calculations for the 1 mg/kg dosing should be based on the body weight, assessed at either the day of dosing, the start of each cycle, or the last recorded weight and if the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, then the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no other dose modifications allowed.

7.4.2.2 Dose Reductions for Investigator's Choice Chemotherapy

Chemotherapy dose reductions are permanent; once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles. Any participant with two prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Chemotherapy - Dose Reductions for Hematologic Toxicity

Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. After the first treatment administration, growth factors may be used to assist hematologic recovery.

Chemotherapy - Dose Reductions for Non- Hematologic Toxicities

All dose reductions should be made based on the worst grade toxicity. Participants experiencing toxicity meeting dose-delay criteria should have their chemotherapy delayed until retreatment criteria are met (per Section 7.4.5).

For FOLFOX

Recommended dose modifications of FOLFOX are provided in Table 7.4.2.2-1 and Table 7.4.2.2-2. Modifications may be made as per local standards.

Table 7.4.2.2-1: Recommended Dose Modifications of FOLFOX

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2 continuous infusion over 46-48 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2 continuous infusion over 46-48 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2 continuous infusion over 46-48 hours

Table 7.4.2.2-2: Dose Modifications of FOLFOX for selected AEs

Toxicity	Definition	During a course of therapy	Dose adjustment for next treatments
Neutropenia	Grade 3 or greater	Interrupt until resolved to Grade 2	Dose level -1 *If treatment delayed for 4 consecutive weeks, discontinue all treatment
Thrombocytopenia	Grade 2	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 2 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 3	Interrupt until resolved to Grade 1	Dose level -1 *If Grade 3 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1
	Grade 4	Interrupt until resolved to Grade 1	Dose level -2 *If Grade 4 persists > 7 days, oxaliplatin reduced by 2 dose levels when platelets improve to Grade 1 *If Grade 4 with bleeding, discontinue oxaliplatin
Neurologic toxicity	Grade 2 peripheral sensory neuropathy	Interrupt until resolved to Grade 1 or management as per institutional standard	Oxaliplatin dose -1 Continue 5-FU and leucovorin *If oxaliplatin delayed for neurologic toxicity for 4 consecutive weeks, discontinue oxaliplatin, continue 5-FU and leucovorin
	Grade 3 or greater peripheral sensory neuropathy	Discontinue oxaliplatin	Continue 5-FU and leucovorin
Gastrointestinal toxicities	Grade 2 or greater diarrhea	Interrupt until resolved to Grade 1	Dose level -1 If dose delayed for diarrhea for 4 consecutive weeks, discontinue all treatment

For toxicities not listed above, dose modifications are permitted per local standards. Participants may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time.

For FOLFIRI

Recommended dose modifications of FOLFIRI are provided in Table 7.4.2.2-3 and Table 7.4.2.2-4. Modifications may be made as per local standards.

Table 7.4.2.2-3: Recommended Dose Modifications of FOLFIRI

Drug	Starting Dose	Dose Modification	
		Dose Level - 1	Dose Level - 2
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/ continuous infusion over 46 hours	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/ continuous infusion over 46 hours	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/ continuous infusion over 46 hours

Table 7.4.2.2-4: Dose modifications of FOLFIRI for selected AEs

Toxicity CTCAE Grade[a]	
Neutropenia/Thrombocytopenia	
Grade 1	Maintain dose level
Grade 2	Reduce 1 dose level
Grade 3	Omit dose until resolved to ≤ Grade 2, then reduce 1 dose level
Grade 4	Omit dose until resolved to ≤ Grade 2, then reduce 2 dose levels
Neutropenic fever	Omit dose until resolved, then reduce 2 dose levels
Diarrhea	
Grade 1	Delay dose until resolved to baseline, then give same dose
Grade 2	Omit dose until resolved to baseline, then reduce 1 dose level
Grade 3	Omit dose until resolved to baseline, then reduce 1 dose level
Grade 4	Omit dose until resolved to baseline, then reduce 2 dose levels
Other non-hematologic toxicities[b]	
Grade 1	Maintain dose level
Grade 2	Reduce 1 dose level
Grade 3	Omit dose until resolved to ≤ Grade 2, then reduce 1 dose level
Grade 4	Omit dose until resolved to ≤ Grade 2, then reduce 2 dose levels
	For mucositis/stomatitis decrease only FU, not irinotecan

[a] National Cancer Institute Common Toxicity Criteria

[b] Excludes alopecia, anorexia, asthenia

A reduced irinotecan starting dose should be considered for patients who have experienced prior haematologic or gastrointestinal toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on a patient's tolerance of the treatment.

For Bevacizumab:

Dose modifications or delay are allowed per institutional standards. Recommended dose modifications for proteinuria are summarized in Table 7.4.2.2-5.

Table 7.4.2.2-5: Recommended Guidelines for Management of Proteinuria

Grade	Description	Management	
Grade 1	1+ protein on urinalysis, or 0.15 to 1g of protein in 24hrs urine collection, or 150 to 1000 mg/g if UPCR is used to assess the proteinuria	Continue Bevacizumab	
Grade 2	2+ or 3+, or 1 to 3.4g/24hrs, or 1000 to 3400 mg/g	Give Bevacizumab and collect 24 hour urine or test UPCR before the next cycle	Resume Bevacizumab only if < 2g/24hours, or < 2000 mg/g If not < 2g/24h, or < 2000 mg/g for 3 months, discontinue Bevacizumab
Grade 3	Urinary protein ≥ 3.5 g/24hrs, or ≥ 3500 mg/g	Discontinue Bevacizumab	

UPCR, urine protein to creatinine ratio

For Cetuximab:

Dose modifications or delay are allowed per institutional standards. For Infusion-related Reactions recommended dose modifications are summarized in Table 7.4.2.2-6:

Table 7.4.2.2-6: Cetuximab dose modifications for infusion-related reactions

Infusion-related reaction toxicity CTCAE Grade[a]	Management
Grade 1 or 2 and non-serious Grade 3	Reduce the infusion rate by 50%
Serious infusion reactions, requiring medical intervention and/or hospitalization	Permanently discontinue cetuximab

[a] National Cancer Institute Common Toxicity Criteria

Skin reactions are very common and treatment interruption or discontinuation may be required. Cetuximab dose modifications for the management of dermatologic toxicity are summarized in Table 7.4.2.2-7 and Table 7.4.2.2-8.

Table 7.4.2.2-7: Cetuximab dose modifications for all grades of skin toxicity

Cetuximab Dose Modification Guidelines for Rash toxicity CTCAE Grade[a]	Management
Grade 1	Continue Cetuximab
Grade 2	Continue Cetuximab
Grade 3	Delay Cetuximab (continue other chemotherapy)
Grade 4	Discontinue Cetuximab permanently

[a] National Cancer Institute Common Toxicity Criteria

Table 7.4.2.2-8: Cetuximab dose modifications for Grade 3 skin toxicity

Occurrence of ≥ Grade 3 toxicity	Cetuximab dose once resolved to ≤ Grade 2[a]
1st Occurrence	Resume at full dose
2nd Occurrence	400 mg/m^2
3rd Occurrence	300 mg/m^2
4th Occurrence	Discontinue Cetuximab

[a] If skin toxicity has not resolved to Grade 2 or better within 3 weeks, discontinue cetuximab.

7.4.3 Criteria to Resume Treatment

7.4.3.1 Criteria to Resume Treatment in Arm A, Arm B or Crossover Cohort

Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value and meet the requirements per Table 7.4-1.

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

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

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

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

When criteria to resume treatment are met, resume both nivolumab and ipilimumab on the same day unless the investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone. Ipilimumab is not permitted to continue on study after nivolumab is discontinued.

7.4.4 Management Algorithms for Nivolumab and Ipilimumab

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered IO agents, and the management algorithms in Appendix 5 provide guidance on assessing and managing the following groups of AEs:

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

7.4.5 Criteria to Resume Treatment in Arm C

Treatment resumption in arm C to be guided by institutional standards. When resuming investigator's choice chemotherapy treatment, please follow the dose reduction recommendations in Section 7.4.2.2.

If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to investigator's choice chemotherapy to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay, unless it is determined by the treating investigator that the patient might benefit from continuation of the component. If treatment was delayed for more than 42 days (6 weeks) the approval of medical monitor is required.

7.4.6 Treatment of Treatment-related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions.

If an infusion-related reaction occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5) guidelines.

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

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

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

For Grade 2 symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

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

permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability as well as the participant's medical records and eCRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.4)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer)

- Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) within 100 days post last dose of nivolumab without or with ipilimumab.
  - 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 therapy is unknown.
- Concomitant use of non-topical medications known to be a strong inducers or inhibitors of CYP3A4, or strong inhibitors of UGT1A1 is prohibited in participants receiving irinotecan.
- Ongoing treatment with aspirin (>325 mg per day) or other medications known to predispose participants to gastrointestinal ulceration is prohibited for participants receiving bevacizumab.
- Also refer to local institutional guidelines and/or product labels of SOC components for other possible prohibited and/or restricted treatments.
- Caution should be exercised in participants treated with oxaliplatin who concurrently receive medicinal products known to prolong the QT interval (refer to local standards and/or www.crediblemeds.org).

7.7.2 Other Restrictions and Precautions

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

7.7.3 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in participants with residual disease and render the participant free of macroscopic disease. Participants randomized in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 24 tumor imaging assessments. If additional tumor shrinkage is noted compared to the tumor imaging assessments at Week 18, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Participants with a confirmed PR who go on to have surgical resection of remaining disease will be considered a PR. Participants with SD who go on to have surgical resection of remaining disease will be considered a SD. Participants may continue treatment after surgery. Tumor tissue of any resected solitary lesion should be submitted to BMS (see Section 9.8). 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.

Some patients treated with chemotherapy may have complete pathological response (pCR) on pathological assessment following surgery with curative intent (defined in Appendix 13).

Similarly, evidence accumulates suggesting that some patients with long-standing radiologic stable disease or partial response while on or following completion of immunotherapy may have pCR after undergoing surgery with curative intent. Exploratory analyses to assess the rate of pathological complete response in patients undergoing surgery and recurrence-free survival will be conducted.

7.7.4 Permitted Therapies

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

7.7.5 Palliative Local Therapy

Participants requiring palliative local therapy (radiotherapy or palliative surgical resection) should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per study defined response criteria is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression in order to resume immunotherapy after palliative local therapy. The potential for overlapping toxicities with radiotherapy and nivolumab/nivolumab plus ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. If palliative radiotherapy is required, then study drugs should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs 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. Participants receiving limited field palliative radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion.

7.7.6 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population.

In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

7.8 Post Study Drug Access

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment **for the maximum treatment duration specified in protocol Section 7.1.1**. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab and/or ipilimumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Documented disease progression (or documentation of further progression for participants receiving treatment beyond progression)
- Additional protocol-specified reasons for discontinuation (see Sections 8.1.1 and 8.1.2).

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy. See Appendix 9 for country-specific requirements.

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

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

8.1.1 Nivolumab and/or Ipilimumab Dose Discontinuation (Arm A, B or Crossover Cohort)

Table 7.4-1 provides criteria for nivolumab or nivolumab plus ipilimumab discontinuation due to immune-mediated AE.

In addition, treatment should be discontinued for:

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study treatment dosing.
- Any event that leads to delay in dosing as per table below:

• **Dosing schedule**	• **Delay in dosing that requires treatment discontinuation**
• Q2W	• > 6 weeks
• Q3W	• > 8 weeks
• Q4W	• > 10 weeks
• Q6W	• > 14 weeks

The following exceptions apply:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is an overlap among the discontinuation

criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant meets the criteria for discontinuation of ipilimumab but not nivolumab, treatment with nivolumab may not resume until the AE/SAE has fully resolved and the participant has discontinued steroids, if they were required for treatment of the AE/SAE. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at the dose according to the treatment schedule (Table 7.1.2-2)

Participants receiving nivolumab plus ipilimumab treatment, who meet criteria for treatment discontinuation and an investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

8.1.2 Investigator's Choice Chemotherapy Dose Discontinuation (Arm C)

Except where specified below, the medications in the SOC chemotherapy regimen should be discontinued for any of the following:

- Any Grade ≥ 4 drug-related peripheral neuropathy requires discontinuation of oxaliplatin. In case of persistent Grade 3 drug-related paraesthesia, oxaliplatin should be discontinued.
- Any Grade ≥ 3 drug-related mucocutaneous reaction possibly attributable to leucovorin requires permanent discontinuation.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 × upper limit of normal (ULN) for > 2 weeks*
  - AST or ALT > 10 × ULN*
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2× ULN*

*In most indicated cases of AST or ALT elevations permanent discontinuation of study treatment is required. This may not be applicable for participants with elevated liver enzymes at baseline. For such cases as well as for situations when the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor must occur.

- Any oxaliplatin-related decrease in creatinine clearance to < 30 mL/minute (using the Cockroft Gault formula) requires discontinuation of oxaliplatin.
- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.

- If any drug-related toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the participant might benefit from continuation of the component.
- In case of unexplained drug-related respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Treatment with **bevacizumab** must be permanently discontinued according to the bevacizumab package insert including the following:

- Grade 4 drug-related hypertension including hypertensive encephalopathy
- Grade 3-4 drug-related hemorrhage
- Grade 4 drug-related non-pulmonary or non-CNS hemorrhage
- Grade ≥ 1 drug-related pulmonary or CNS hemorrhage
- Drug-related arterial thromboembolic event (any grade)
- Any grade of drug-related congestive heart failure
- Participants who develop drug-related gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ
- Grade 4 drug-related venous thromboembolic event (VTE), including pulmonary embolism
- Drug-related wound dehiscence (any grade –requiring medical or surgical therapy)
- Drug-related reversible posterior leukoencephalopathy (any grade - confirmed by MRI)
- Other unspecified bevacizumab related AE's (Grade 4)

Treatment with **cetuximab** must be permanently discontinued according to the cetuximab package insert including the following:

- Confirmed drug-related interstitial lung disease (ILD)
- Serious drug-related infusion reactions, requiring medical intervention and/or hospitalization
- Grade 4 drug-related skin toxicity

For toxicities not listed above, the treating investigators can decide to discontinue any individual chemotherapy agent or all chemotherapy agents if it is not the best interest in the participant per the local standards.

Dosing delays lasting > 6 weeks from the previous dose that occur for drug-related and non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1.3 Treatment Beyond Progression for Participants in the Arms A, B or Crossover Cohort

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[40]

Participants treated with nivolumab or nivolumab plus ipilimumab combination will be permitted to continue treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator as long as they meet the following criteria:

1) Investigator-assessed clinical benefit
2) Tolerance of study treatment
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) Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.
6) Participant has not reached maximum treatment duration as defined in protocol Section 7.1.1
7) Approval from BMS medical monitor or designee

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

Radiographic assessment/scan(s) should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab or nivolumab plus ipilimumab.

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

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

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

10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.4 Post Study Treatment Study Follow-up

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

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

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening/baseline evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization, or treatment in the Crossover Cohort. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

Testing for asymptomatic SARS-CoV-2 infection, for example by RT-PCR or viral antigen, is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be eligible for the study after recovery from infection or completion of quarantine period in case of asymptomatic infection/potential exposure.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

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

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

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab for BICR at any time during the study. Sites should be qualified prior to scanning the first study participant and understand the image acquisition guidelines and submission process as outlined in the CA2098HW Imaging Manual to be provided by the core lab.

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

Screening and on study images should be acquired as outlined in the Schedule of Activities (Section 2). To facilitate the transition of the imaging acquisition to be unified across study participants schedule from every 8 weeks (12 weeks in the Crossover cohort) to every 16 weeks (during year 3) or 24 weeks (during year 4 and beyond) from randomization, the collection of imaging at additional timepoints maybe required. This will depend on the timing of approval of the reduced imaging acquisition schedule at study sites and upcoming timepoint of tumor assessment. Additional details are provided in a memo to the sites.

Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor assessments at other timepoints may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-Ray and bone scans that clearly demonstrate interval progression of disease, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, radiographs do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same

scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

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

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

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

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

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

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

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

9.1.1.2 BICR Assessment of Progression

Sites should submit all scans to a BICR, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans, and remain blinded to treatment arm and investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor, so that the BICR assessment of progression can be expedited. The BICR review will be completed and limited results provided

to the site as specified within the imaging vendor document, provided there are no pending queries to the site.

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

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.

BICR confirmation of disease progression per RECIST 1.1 is mandatory before enrollment to crossover cohort. The participant will be re-baselined based on the investigator's assessment of the scans with which BICR progression was confirmed. If additional scans were obtained after BICR-assessed progression but before the beginning of study therapy in the Crossover Cohort, these scans should be used as crossover baseline scans. Tumor assessments in participants in crossover cohort will be done by BICR and should comply with the requirements outlined in this Section of the protocol.

9.1.1.3 Imaging and Clinical Assessment

Tumor assessments for all participants (arm A, B, C, and crossover cohort) should continue as per protocol even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator per study design using RECIST 1.1 criteria. Investigators will also report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST 1.1 criteria (See Appendix 7 for specifics of RECIST 1.1 criteria to be utilized in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response of SD requires a minimum of 35 days on study from date of randomization to the date of the first imaging assessment.

9.1.2 Patient-Reported Outcomes

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

The European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and 29-item Colorectal-specific (QLQ-CR29) modules will be used to assess the effects of cancer and treatment on symptoms, functioning and well-being. The EORTC QLQ-C30 is one of the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive,

emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 are transformed to a 0-100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. The EORTC QLQ-CR29 comprises colorectal cancer-specific domains and symptoms, including sexual function-, stoma-, and bowel function-related items. [78,79]

The 3-level version of the EQ-5D (EQ-5D-3L) will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.

The questionnaires will be provided in the participant's preferred language when available and the EQ-5D-3L may be administered by telephone during survival follow up using a script for telephone administration.

The EQ-5D-3L and the EORTC QLQ-C30 and QLQ-CR29 will be collected for all participants per the schedule provided in Section 2.

9.2 Adverse Events

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

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

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

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

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE (with the exception of non-serious AEs related to SARS-CoV-2 infection) information should begin at initiation of study treatment and continue during the treatment period and for a minimum of 100 days following discontinuation of study treatment, at the time points specified in the Schedule of Activities (Section 2). 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 participants. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

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

- Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of discontinuation of dosing. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported.
- For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.
- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2) and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, until the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Regulation 536/2014 and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected

Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable. Study treatment must be permanently discontinued where locally mandated, see Appendix 9 for country-specific requirements.

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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

   AND

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

   AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2). A systematic screening for DPD deficiency has to be performed during screening period for participants who have not received prior therapy or receive one line of prior therapy if locally required. QT prolongation and ventricular arrhythmias, including fatal torsades de pointes, have been reported with oxaliplatin. Correct electrolyte abnormalities (particularly potassium and magnesium) prior to initiating oxaliplatin and periodically during treatment. In the event of an extension of the QT/QTc interval, including the prolongation of the QT/QTc interval > 500 msec, implement close and adapted ECG monitoring (continuously) in a hospital until the advice of a cardiologist is available, and permanently discontinue oxaliplatin. Follow local standards for the management of QT interval prolongation.

9.4.1 Physical Examinations

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.

Refer to Schedule of Activities in Section 2.

9.4.2 Vital signs

Vital signs are to be collected within 14 days prior to randomization, and collected just prior to each dose of study medication. Refer to Schedule of Activities in Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities in Section 2. Additional monitoring of electrocardiograms is to be performed in accordance with local standards in participants with congestive heart failure, bradyarrhythmias, and electrolyte abnormalities, and in participants taking drugs known to prolong the QT interval.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Amylase Lipase Creatinine Blood Urea Nitrogen (BUN) or serum urea Glucose (fasting is not reqired) PTT/INR - screening and as clinically indicated during bevacizumab treatment PTT - screening	Albumin - screening only Sodium Potassium Chloride Calcium Magnesium screening and during treatment if study treatment contains cetuximab Phosphorus Blood uracil (if locally required) - screening only
Endocrine function testing	
Screening - TSH, free T3 and free T4. Additional tests (e.g. ACTH, cortisol, etc) per local requirements to be performed. **On treatment** - TSH, with reflexive fT3 and fT4 if TSH is abnormal. Additional tests (e.g. ACTH, cortisol, etc.) per local requirements should be performed if clinically indicated.	

Follow up - TSH, free T3, free T4. Additional tests (e.g. ACTH, cortisol, etc.) per local requirements should be performed if clinically indicated.	
Urinalysis	
Protein Glucose Blood	Leukocyte esterase Specific gravity pH
Serology	
Hepatitis B and Hepatitis C, (HBV sAg, HCV antibody or HCV RNA), - screening only. If anti-HCV test is positive, then HCV RNA is mandatory. SARS-CoV-2 (screening, Cycle 6 Day 1 and every 6 cycles)	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening (only required to confirm menopause in women < age 55)	
CEA and CA19-9 Assessment – during screening, and at re-staging timepoints	
DPD-deficiency testing per local standards	

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics and Immunogenicity Assessments

Table 9.5-1 provides a detailed sampling schedule for pharmacokinetic and immunogenicity measurements for nivolumab for participants in arm A. Table 9.5-2 and Table 9.5-3 provide a detailed sampling schedule for pharmacokinetic and immunogenicity measurements for nivolumab and ipilimumab for participants in arm B and the Crossover Cohort, respectively. All on treatment PK timepoints are intended to align with days on which study drug is administered. Further details of sample collection, processing, and shipment will be provided in the laboratory manual.

Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all pre-dose and end of infusion-PK (EOI-PK) samples. Please ensure accurate documentation of the time and date of sample collection. Samples will be evaluated for development of anti-drug antibody (ADA). Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow-up on suspected immunogenicity-related AEs.

Table 9.5-1: PK Sampling- Pharmacokinetic & Immunogenicity Sampling Schedule - Nivolumab Monotherapy (Arm A)

Study Day of Sample Collection Cycles 1-2 = 6 weeks each Cycle 3 and beyond = 4 weeks each	Event	Time (Relative To Start of Nivolumab Infusion) Hour: Min	Pharmacokinetic Serum Sample for Nivolumab	Immunogenicity Serum Sample for Nivolumab
Cycle 1 Day 1	Predose[a]	0:00	X	X
Cycle 1 Day 29	Predose[a]	0:00	X	X
Cycle 3 Day 1	Predose[a]	0:00	X	X
Cycle 3 Day 1	End of Infusion[b]	0:30	X	
Cycle 6 Day 1	Predose[a]	0:00	X	X
Day 1 every 6 cycles starting at Cycle 12 (Cycle 12, Cycle 18, Cycle 24, etc) up to 2 years of treatment	Predose[a]	0:00	X	X

[a] Predose samples should be collected just prior to the start of infusion on the day the study drug is administered. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected

[b] End of infusion (EOI) sample should be taken immediately prior to the stopping of nivolumab infusion, preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

Table 9.5-2: PK Sampling- Pharmacokinetic & Immunogenicity Sampling Schedule - Nivolumab plus Ipilimumab Combination Therapy (Arm B)

Study Day of Sample Collection Cycles 1-2 = 6 weeks each Cycle 3 and beyond = 4 weeks each	Event	Time (Relative to Start of Nivolumab Infusion) Hour: Min	Pharmacokinetic Serum Sample for Nivolumab	Immunogenicity Serum Sample for Nivolumab	Pharmacokinetic Serum Sample for Ipilimumab	Immunogenicity Serum Sample for Ipilimumab
Cycle 1 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 1 Day 22	Predose[a]	0:00	X	X	X	X
Cycle 2 Day 22	Predose[a]	0:00	X	X	X	X
Cycle 3 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 3 Day 1	End of Infusion[b]	00:30	X			
Cycle 6 Day 1	Predose[a]	0:00	X	X	X	X
Day 1 every 6 cycles starting at Cycle 12 (Cycle 12, Cycle 18, Cycle 24, etc) up to 2 years of treatment	Predose[a]	0:00	X	X		

[a] On study days where nivolumab and ipilimumab are coadministered, the predose samples for both nivolumab and ipilimumab should be collected just prior to the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[b] End of infusion (EOI) sample should be taken immediately prior to the stopping of nivolumab infusion, preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

Table 9.5-3: PK Sampling- Pharmacokinetic & Immunogenicity Sampling Schedule - Crossover Cohort

Study Day of Sample Collection Cycles 1-2 = 6 weeks each Cycle 3 and beyond = 4 weeks each	Event	Time (Relative to Start of Nivolumab Infusion) Hour: Min	Pharmacokinetic Serum Sample for Nivolumab	Immunogenicity Serum Sample for Nivolumab	Pharmacokinetic Serum Sample for `Ipilimumab	Immunogenicity Serum Sample for Ipilimumab
Cycle 1 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 1 Day 15	Predose[a]	0:00	X	X	X	X
Cycle 2 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 3 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 3 Day 1	End of Infusion[b]	--[c]	X		X	
Cycle 6 Day 1	Predose[a]	0:00	X	X	X	X
Cycle 7 Day 1	Predose[a]	0:00	X	X	X	X
Day 1 every 6 cycles starting at Cycle 12 (Cycle 12, Cycle 18, Cycle 24, etc) up to 2 years of treatment	Predose[a]	0:00	X	X	X	X

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

[b] EOI samples for nivolumab and ipilimumab should be collected together at the end of (preferably, within 2 minutes prior to the end of) ipilimumab infusion. If the end of infusion is delayed beyond the nominal infusion duration, the collection of these samples should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] Since both nivolumab and ipilimumab EOI samples will be collected at the end of Ipilimumab infusion, the relative time will be 1:30 for nivolumab and 0:30 for ipilimumab EOI sample.

9.6 Pharmacodynamics

See Section 9.8.

9.7 Pharmacogenomics

See Section 9.8.

9.8 Biomarkers

Biomarker sample collection schedules are presented in Table 9.8-1 for nivolumab monotherapy (arm A) and investigator's choice chemotherapy (arm C), Table 9.8-2 for nivolumab plus ipilimumab combination (arm B), and Table 9.8-3 for the Crossover Cohort.

Table 9.8-1: Biomarker Sampling Schedule - Nivolumab Monotherapy (Arm A) and Investigator's Choice Chemotherapy (Arm C)

Study Day of Sample Collection **Cycles 1 -2 (cycle = 6 weeks)** **Cycles 3 to EOT (cycle = 4 weeks)**	**Tumor**	**Whole Blood**	**Plasma**	**Serum**	**MDSC**	**PBMC**	**Microbiome**	**SARS-CoV-2 Serology**
Screening	X						X[a]	X
Cycle 1 Day 1		X	X	X	X	X		
Cycle 1 Day 15			X	X	X	X		
Cycle 1 Day 22-28	X[b]							
Cycle 2 Day 1			X	X	X	X	X[c]	
Cycle 3 Day 1			X	X	X			
Cycle 4 Day 1			X					
Cycle 6 Day 1 and every 2 cycles			X					
Cycle 6 Day 1 and every 6 cycles[d]								X
Upon Progression	X[b]		X	X	X	X	X	
Follow-Up Visit 1								X

[a] Stool should be collected within 7 days prior to first dose.

[b] On-treatment (1 week after 2nd dosing and prior to the 3rd dosing, i.e. between Day 22-28 of Cycle 1) and at progression (PD + 14 days) tumor biopsy are optional but strongly encouraged to understand the resistance/response to nivolumab or SOC treatment. The biopsy upon progression on arm C is mandatory, if medically feasible, for enrollment to Crossover Cohort. If biopsy is performed, biopsy samples must be submitted. If biopsies/surgical resection are done at any other time on treatment, tissue samples should be submitted as well.

[c] Stool should be collected within 3 days prior to dosing.

[d] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6 month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 week after infection time points.

Abbreviations: MSDC, myeloid-derived suppressor cells; PBMC, peripheral blood mononuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOC, standard of care.

Table 9.8-2: Biomarker Sampling Schedule - Nivolumab plus Ipilimumab Combination Therapy (Arm B)

Study Day of Sample Collection **Cycles 1 -2 (cycle = 6 weeks)** **Cycles 3 to EOT (cycle = 4 weeks)**	**Tumor**	**Whole Blood**	**Plasma**	**Serum**	**MDSC**	**PBMC**	**Microbiome**	**SARS-CoV-2 Serology**
Screening	X						X[a]	X
Cycle 1 Day 1		X	X	X	X	X		
Cycle 1 Day 22			X	X	X	X		
Cycle 1 Day 29-35	X[b]							
Cycle 2 Day 1			X	X	X	X	X[c]	
Cycle 3 Day 1			X	X	X			
Cycle 4 Day 1			X					
Cycle 6 Day 1 and every 2 cycles			X					
Cycle 6 Day 1 and every 6 cycles[d]								X
Upon Progression	X[b]		X	X	X	X	X	
Follow-Up Visit 1								X

[a] Stool should be collected within 7 days prior to first dose.

[b] On-treatment (1 week after 2nd dosing and prior to the 3rd dosing, i.e. between Day 29-35 of Cycle 1) and at progression (PD + 14 days) tumor biopsy are optional but strongly encouraged to understand the resistance/response to nivolumab plus ipilimumab treatment. If biopsy is performed, biopsy samples must be submitted. If biopsies/ surgical resection are done at any other time on treatment, tissue samples should be submitted as well.

[c] Stool should be collected within 3 days prior to dosing.

[d] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6 month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 week after infection time points.

Abbreviations: MSDC, myeloid-derived suppressor cells; PBMC, peripheral blood mononuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 9.8-3: Biomarker Sampling Schedule - Crossover Cohort

Study Day of Sample Collection **Cycles 1 -2 (cycle = 6 weeks)** **Cycles 3 to EOT (cycle = 4 weeks)**	**Tumor**	**Whole Blood**	**Plasma**	**Serum**	**MDSC**	**PBMC**	**Microbiome**	**SARS-CoV-2 Serology**
Baseline	X						X[a]	X
Cycle 1 Day 1		X	X	X	X	X		
Cycle 1 Day 15			X	X	X	X		
Cycle 1 Day 22-28	X[b]							
Cycle 2 Day 1			X	X	X	X	X[c]	
Cycle 3 Day 1			X	X	X			
Cycle 4 Day 1			X					
Cycle 6 Day 1 and every 3 cycles			X					
Cycle 6 Day 1 and every 6 cycles[d]								X
Upon Progression	X[b]		X	X	X	X	X	
Follow-Up Visit 1								X

[a] Stool should be collected within 7 days prior to first dose.

[b] On-treatment (1 week after 2nd dosing and prior to the 3rd dosing, i.e. between Day 22-28 of Cycle 1) and at progression (PD + 14 days) tumor biopsy are optional but strongly encouraged to understand the resistance/response to nivolumab plus ipilimumab treatment. If biopsy is performed, biopsy samples must be submitted. If biopsies/ surgical resection are done at any other time on treatment, tissue samples should be submitted as well.

[c] Stool should be collected within 3 days prior to dosing.

[d] Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection. If a documented or suspected SARS-CoV-2 infection occurs within 4 weeks of the 6 month sampling time point, a single serum sample will be collected to satisfy the requirements for both the every 6 month and approximately 4 week after infection time points.

Abbreviations: MSDC, myeloid-derived suppressor cells; PBMC, peripheral blood mononuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

9.8.1 Tissue biomarkers

Tissue samples will be collected for MSI/MMR and additional biomarker assessment. Either a FFPE tissue block (preferred) or unstained tumor tissue sections (minimum of 30 positively charged slides), from primary or metastatic site, must be submitted to the central laboratory. Tumor tissue specimen must meet either of the criteria below:

i) Obtained within 3 months of enrollment with no intervening systemic anti-cancer treatment between time of acquisition and randomization AND this must be the same tissue sample as was used for local MMR/MSI testing;

OR

ii) If above is not available, archival tissue can be accepted if the same tissue was used for local MMR/MSI testing.

Central lab must provide IRT with confirmation of receipt of evaluable tumor tissue prior to randomization. Tumor tissue should be excisional, incisional or core needle biopsies or surgical specimens. Fine needle biopsies are not acceptable. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone samples are also not acceptable. These requirements are crucial to fulfill the commitment to develop in vitro diagnostic devices for dMMR/MSI-H detection in mCRC and ensure the quality of the tissue for biomarker analyses. In addition, peripheral blood and stool samples will be collected. Biomarker analyses will aim at identifying potential predictive biomarkers of nivolumab monotherapy, and combination therapy of nivolumab with ipilimumab treatment and furthering our understanding of CRC disease biology in relation to checkpoint blockade therapy.

Biomarker analyses of tumor samples may include but are not be limited to:

- MSI/MMR: In association with the Accelerated Approval of nivolumab monotherapy and nivolumab plus ipilimumab combination therapy in this indication, BMS is required to fulfill a post-marketing commitment with the US FDA to support labeling of an immunohistochemistry based in vitro diagnostic, as well as a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab and nivolumab in combination with ipilimumab for patients with tumors that are dMMR/MSI-H.
- Gene expression profiling (GEP) will be performed to examine potential signatures that may predict or associate with response/resistance to therapy. Potential signatures may include but not be limited to:
  - CRC subtyping signatures. Different CRC subtypes may respond differently to checkpoint blockade because of the different molecular biology underlying each subtype. Consensus molecular subtype (CMS) has categorized CRC into 4 different CMSs, with dMMR/MSI-H CRC falling under CMS1. [80] However, even within the dMMR/MSI-H CRCs, differential outcomes were observed in CheckMate-142 (CA209142). Potential subtyping signatures that can predict response in the dMMR/MSI-H population may be explored.
  - Signatures of the tumor microenvironment. The tumor immune microenvironment plays a pivotal role in tumorigenesis and is important in determining response to checkpoint blockade therapy. Signatures of the tumor immune microenvironment, such as various

inflammatory signatures, may be explored to examine their association with response to nivolumab or nivolumab plus ipilimumab therapy.

- Tumor Mutational Analysis:
  - TMB (tumor mutational burden) has been associated with response to checkpoint blockade therapy in lung cancer. The CA209026 study evaluated 1L NSCLC patients treated with nivolumab versus chemotherapy. For patients with higher TMB, higher response rates and longer progression-free survival were observed in the nivolumab treated group compared to the chemotherapy group.[81] The recent evaluation of TMB and clinical response in different tumor types has also suggested a correlation between TMB and objective response rate across different disease indications.[82] TMB correlation with response will be examined further in the dMMR/MSI-H CRC indication in this study. In addition, neo-antigen profiling may be performed based on the predicted affinity of the detected mutations to MHC proteins and correlated with response.
  - Other genomic/genetic alterations of interest, such as BRAF, RAS, and other genes involved in CRC biology may be analyzed as well.
- For gene expression profiling and tumor mutational or genetic alteration analyses, DNA and/or RNA isolated from the tumor tissue collected at baseline and on treatment may be analyzed using sequencing techniques including, but not limited to, whole exome and whole transcriptome sequencing.
- Characterization of the tumor microenvironment. A growing body of evidence suggests the importance of tumor associated immune cells in the tumor microenvironment. Immunoscore has been shown to be prognostic in both dMMR/MSI-H and MSS CRC.[83] Immunohistochemistry (IHC) or other technologies will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumor tissue before and after exposure to therapy. These analyses may include, but not necessarily be limited to PD-L1, PD-1, CD3, CD8, MHC-I, MHC-II, and LAG3.

9.8.2 Peripheral Blood

A variety of factors that may impact the immunomodulatory properties and efficacy of study treatment will be investigated in peripheral blood specimens taken from all participants prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Several analyses will be completed and are described briefly below.

9.8.3 Soluble Biomarkers

Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified. Analyses may include, but not necessarily be limited to, Carcinoembryonic antigen (CEA), CA19-9, IL2Ralpha and IL-8. Collected serum samples may also be used for the assessment of tumor antigen-specific responses elicited following study treatment to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens may be assessed.

Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or IgG) to explore potential association with safety, efficacy, and/or immune biomarkers.

9.8.3.1 Immunophenotyping

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

9.8.3.2 Whole Blood for Germline DNA

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for genetic analyses and to serve as a reference for tumor genomic testing. Whole blood DNA may be analyzed using sequencing techniques including, but not limited to, whole exome sequencing.

9.8.3.3 Myeloid Derived Suppressor Cells

Myeloid derived suppressor cells (MDSCs) are an immune cell population capable of suppressing T cell activation and proliferation and may potentially affect outcomes to checkpoint blockade therapy.[84] Higher MDSC in peripheral blood was observed in CRC patients compared with healthy individual.[85] MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic changes or associations with outcome.

9.8.3.4 Circulating Tumor DNA Analysis (Plasma) Biomarkers

Peripheral blood samples will be collected to generate plasma for cell free circulating tumor-DNA (ctDNA) analysis. Liquid biopsy, such as ctDNA analysis, offers a non-invasive alternative for monitoring tumor evolution and therapeutic response compared to traditional tissue biopsy.[86] Plasma samples will be collected at baseline and on treatment and upon progression will be analyzed to determine the presence, frequency and genomic profile of ctDNA. Plasma samples may be analyzed using sequencing techniques including, but not limited to, panel-based next-generation sequencing.

9.8.4 Stool Sample Collection

The gut microbiome influences cancer development and response to therapy. The efficacy of cancer immunotherapy with checkpoint blockade could be diminished with the administration of antibiotics. Clinical efficacy has been associated with microbiome composition and the presence of specific microbe species.[87,88,89] The association of microbiome with efficacy and safety will be evaluated using stool samples collected before and during treatment.

9.8.5 Additional Research Collection

This protocol will include residual sample storage for additional research.

[redacted]

For All US sites:

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

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

For non-US Sites

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

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

Sample Collection and Storage

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

Residual tumor tissue and Serum samples from biomarker and PK collections (see Table 9.8.5-1) will also be retained for additional research purposes.

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

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

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

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

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

Table 9.8.5-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
PK	All
Tumor Biopsy	All
Serum samples	All

9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The study will enroll participants irrespective of the line of therapy, however their randomization across study arms will depend on the number of prior lines of systemic treatments they have been exposed. In protocol revision 04, 1L expansion was added and the study has two parts of enrollment. During part 1 enrollment, participants who have received no more than 1 prior line of systemic therapy (0 or 1) will be randomized to nivolumab monotherapy arm (arm A), nivolumab plus ipilimumab combination therapy arm (arm B) or an investigator's choice of chemotherapy arm (arm C) at a 2:2:1 ratio. Participants who have received 2 or more prior lines of systemic therapy will be randomized to arm A or to arm B at a 1:1 ratio. During Part 1 enrollment, of all randomized participants it is expected that proportion of those who have had 0 prior line of systemic therapy (1L) will be approximately 35%, those who had 1 prior line of systemic therapy (2L) will be approximately 35%, and those who have had a least 2 lines of systemic therapy (3L+) will be approximately 30%. Completion of Part 1 enrollment will be triggered based on internal assessments to ensure the randomization of approximately 442 participants with dMMR/MSI-H per central testing, a number pre-specified in protocol revision 03. Part 2 enrollment was added in protocol revision 04 in order to provide appropriate power for PFS comparison among 1L participants between arms B vs C and arms B vs A. Part 2 enrollment will start immediately after the closure of Part 1 enrollment and only 1L eligible participants will be randomized to arms A, B and C at 2:2:1 ratio.

Comparisons of an efficacy endpoint (eg, PFS, ORR, or OS) between a given two arms will be based on concurrently randomized participants to the corresponding two arms, except otherwise specified.

Participants will be enrolled based on local evaluation of their dMMR/MSI-H status but the primary efficacy populations will consist of participants with centrally confirmed dMMR/MSI-H mCRC by either central test (IHC or PCR-based) (Section 5.4.7). It is expected that approximately

15% of the participants may not have their local dMMR/MSI-H mCRC confirmed centrally. The sample size calculation is based on randomized participants with dMMR/MSI-H status confirmed by central tests. Unless otherwise specified, "participants" of Study CA2098HW mentioned in Section 10.1 refer to "randomized participants with dMMR/MSI-H status confirmed by central tests"; clinical outcomes (e.g., "event," "response," etc) of Study CA2098HW mentioned in Section 10.1 refer to those observed among randomized participants with dMMR/MSI-H status confirmed by central tests.

The sample size of this study will be driven by the comparison of the two primary endpoints and the secondary endpoint of PFS comparison between 1L participants randomized to arm B and arm A:

1. PFS comparison between participants randomized to arm B and arm A during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs A in all lines'
2. PFS comparison between participants who have not received prior line of systemic therapy and randomized to arm B and arm C during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs C in 1L'.
3. PFS comparison between participants who have not received prior line of systemic therapy and randomized to arm B and arm A during Part 1 and Part 2 enrollment, hereafter denoted as 'PFS B vs A in 1L'.

The power calculation for the key secondary endpoints will also be discussed in this section.

Generally, in studies with time-to-event type endpoint, the sample size calculation assumes an exponential distribution of the endpoint when treated with chemotherapies. However, in the CA209142 study long-term PFS and survival benefit were observed as it has been observed in multiple studies evaluating immunotherapeutic agents. When treated with nivolumab monotherapy or treated with nivolumab plus ipilimumab, a long lasting plateau towards the end of the Kaplan-Meier (KM) curves of PFS and OS were observed.[29,30,31,32] Recent published results from the Keynote-177 study also demonstrated a long lasting plateau towards the end of KM curve of PFS in the pembrolizumab arm when directly compared to the chemotherapy arm.[1] Based on these data, sample size determination for PFS is calculated by assuming a piecewise exponential distribution in arm A and B and exponential distribution in arm C.

In order to control the overall type I error at 5%, for the purpose of sample size calculation, the alpha is initially split between the two primary endpoints, with 0.6% for PFS B vs A in all lines and 4.4% for PFS B vs C in 1L. The secondary endpoint of PFS B vs A in 1L will be tested hierarchically. The testing procedure for the other secondary endpoints is provided in the protocol Section 10.3.10.

10.1.1 Sample Size Determination of Primary Endpoints

PFS in all lines for comparison between arms B vs A

Initial assumptions

Prior to Revised Protocol 04, based on the observed PFS curve and rates at different time points in the nivolumab monotherapy cohorts of CA209142 (data on file, August 2018 database lock), the PFS distribution for nivolumab monotherapy (arm A) was assumed to be piecewise exponential with the following landmark PFS rates, as presented in Table 10.1.1-1 below.

Since both arm A and arm B are immunotherapies, no delayed separation of PFS KM curves will be expected. A constant hazard ratio (HR) of 0.65 for arm B compared with arm A is assumed which therefore translates to piecewise exponential distribution of PFS in arm B (Table 10.1.1-1). Under these assumptions, the median estimates for PFS is 6 months and 27 months for monotherapy and combination therapy arms, respectively.

Table 10.1.1-1: PFS Rates of Arm A and Arm B in All Lines and Hazard Ratios

Period	Cumulative PFS Rate for Nivolumab (%)	Cumulative PFS Rate for Nivolumab and Ipilimumab Combination (%)	Hazard Ratio
0 - 1 month	93.0	95.4	0.65
3 months	65.0	75.6	0.65
6 months	50.0	63.7	0.65
9 months	45.0	59.5	0.65
12 months	43.0	57.8	0.65
18 months	40.0	55.1	0.65
24 months	36.0	51.5	0.65
36 months	30.0	45.7	0.65
48 months	20.0	35.1	0.65
60 months and after	10.0	22.4	0.65

Abbreviations: PFS, progression free survival

Approximately 354 PFS events will provide about 90% power to detect a HR of 0.65 with an overall type 1 error of 0.006 (two-sided). Under the assumption of a staggered enrollment, it is required to randomize approximately 564 participants to both arm A and B during Part 1 and Part 2 enrollment.

This initial design accounts for one PFS interim look when approximately 80% of the total number of events are observed (approximately 283 events). It is projected that Part 1 enrollment will take approximately 16 months and Part 2 enrollment will take approximately 14 months. The timing of final analysis is projected to be 49 months from the date of first participant being randomized during Part 1 enrollment.

Updated assumptions

In protocol revision 03, the assumed PFS rates in arm A in all lines (Table 10.1.1-1) were from the nivolumab monotherapy cohort of CA209142 based on data with a minimum follow-up of 27.6

months (follow-up duration is defined as clinical cut-off date minus first dose date). At the time of protocol revision 04 development, updated data from the nivolumab monotherapy cohort of CA209142 were available with minimum follow-up of 43 months for nivolumab monotherapy. The updated KM curve of PFS in the monotherapy arm suggested even more flattened tail or higher PFS rates than currently assumed PFS rates in arm A from 18 months onward (Table 10.1.1-1). Meanwhile, the PFS KM curve observed in the pembrolizumab arm of the Keynote-177 study also suggested a similar pattern in 1L setting. Therefore, these newly available data outside of the study suggested a more reliable assumption of PFS rates in arm A as presented in Table 10.1.1-2 and Figure 10.1.1-1. The updated PFS rates of arm A in all lines suggested that the final analysis timing (when at least 354 PFS events are observed) will be delayed to 62 months after first participant randomized during Part 1 enrollment. To ensure a timely readout of PFS in all lines in order to fulfill the PMR, the final analysis of the primary endpoint of PFS B vs A in all lines will be conducted when at least 319 PFS events are observed, which is projected to be approximately 50 months after the first participant is randomized during Part 1 enrollment. A total of 319 PFS events will provide approximately 86% power under the assumption that HR=0.65 for PFS B vs A in all lines with two-sided alpha of 0.006.

Table 10.1.1-2: PFS Rates in Arm A in All Lines Updated Based on Most Recent Data Outside of the Study

Period	Cumulative PFS Rate for Nivolumab (Arm A) (%) Across Lines
0 - 1 month	93.0
3 months	65.0
6 months	50.0
9 months	45.0
12 months	44.0
18 months	43.0
24 months	40.0
30 months	38.0
36 months	35.0
42 months and after	32.0

Abbreviations: PFS, progression free survival

In addition, indirect comparisons between the combination cohort vs monotherapy cohort of the CA209142 study have consistently suggested a lower HR than assumed 0.65 between arms B vs A in the 2L+ setting. In 1L setting, the indirect comparison of PFS from 1L combination cohort of CA209142 and the pembrolizumab monotherapy of the Keynote-177 study also suggested a lower HR than 0.65. Under the assumption that HR=0.635 for PFS B vs A in all lines, the 319 PFS events will provide 90% power for PFS B vs A in all lines. Figure 10.1.1-1 shows the assumed PFS

distribution of arm A and arm B in all lines, under a constant HR of 0.65 and 0.635 for PFS in B vs A.

Overall, with the 564 participants concurrently randomized to arm B and arm A across lines and followed until at least 319 PFS events are observed, it will provide a power of 90% with two-side alpha of 0.006 for HR of 0.635. If PFS B vs C in 1L meets the pre-specified statistical criteria at the interim or final analysis and 0.024 alpha is passed to PFS B vs A in all lines, 319 PFS events will provide approximately 96.8% power with two-sided alpha of 0.03 for HR of 0.635. Details on alpha for this test is described in Section 10.3.10. An interim analysis will be conducted when approximately 85% of the total number of events are observed (approximately 271 events) and after the last participant is randomized during Part 2 enrollment.

PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. Therefore, 0.024 alpha was passed to PFS B vs A in all lines. PFS B vs A in all lines has not been tested yet and is projected to be significantly delayed from protocol assumption. As a result of the PFS events delay, the study-wise final analysis (OS final analyses), defined at the 5 years from the first participant's randomization (Aug-2019), which is around Aug-2024, is no longer feasible because it is prior to the conclusion of its precedents endpoints thus will deviate from the testing strategy (Figure 10.3.10-1). In order to maintain the testing strategy in the pre-planned analysis around Aug-2024, the study-wise final analysis for OS at the 5-year mark is removed and an interim analysis of PFS B vs A in all lines is added at this time. It is projected that the PFS events for Arm B vs A in all lines will reach approximately 240 events (~75% of the total number of events) around Aug-2024. If PFS B vs A in all lines met its pre-specified statistical significance in this IA, the secondary endpoints including OS (IA) are allowed to be tested following the testing strategy. The originally planned PFS IA B vs A in all lines at approximately 271 events will be the second IA after the one around Aug 2024. The target number of events for the PFS FA B vs A in all lines (approximately 319 events) remain unchanged. The final analysis of PFS B vs A in all lines will be conducted when approximately 319 events are observed or 2 years after the last participant from Part 2 enrollment was randomized ("2-year minimum follow-up"), whichever occurs first.

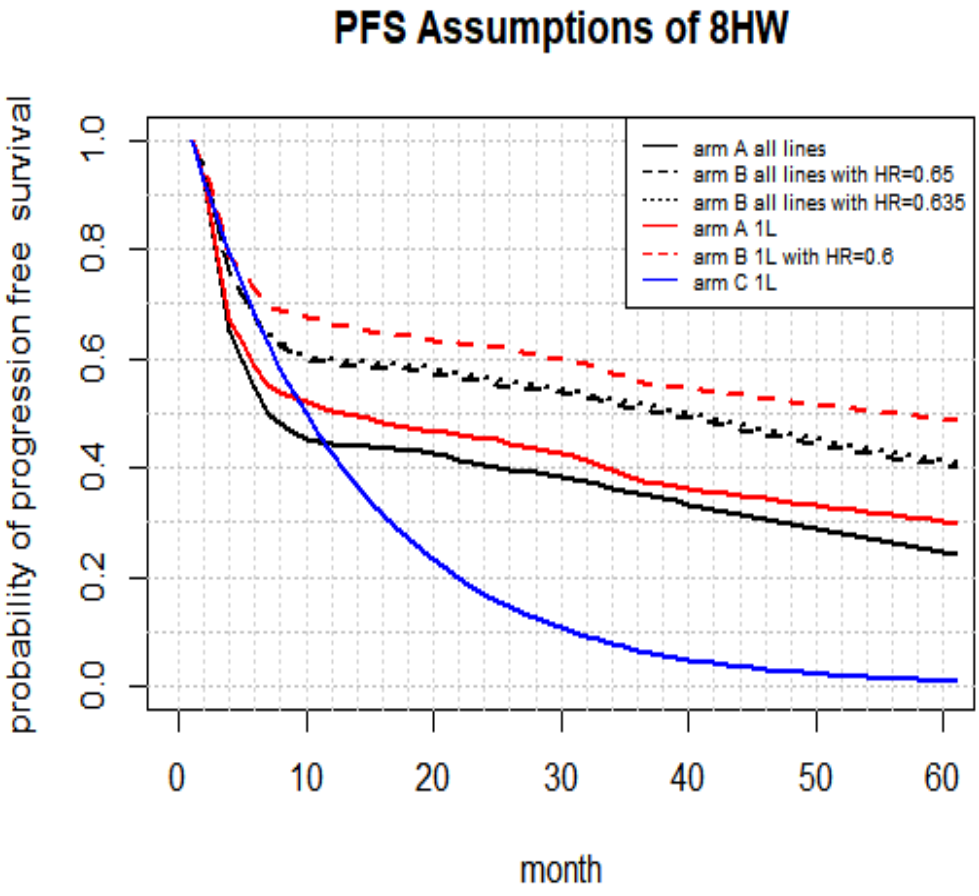
At a 2-year minimum follow-up, the estimated median follow-up will be approximately 4 years, given the long enrollment period. Data from study CA209142 and from an external study of single agent checkpoint inhibitors in 1L MSI-H/dMMR mCRC for which long-term results are available, clearly illustrates flattening of PFS KM curves (for nivo+ipi and nivo [from study CA209142] and single agent checkpoint inhibitors) starting at Month 24.[90,91] Assuming a similar trend in study CA2098HW, a limited accumulation of PFS events is expected beyond the 2-year minimum follow-up for all participants.

Therefore, PFS B vs A in all lines will have 2 IAs (1 at approximately 240 events with a data cut-off around Aug-2024 [newly added] and 1 at approximately 271 events [previously planned]) and a FA (previously planned, but with updated timing: when approximately 319 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first). The second IA will be skipped if the projected time of the second PFS IA B vs A in

all lines is too close to the proposed PFS FA time (eg, less than 6 months apart), or it is projected to be after the proposed PFS FA time.

The significance level for the PFS IA(s) will be determined based on the observed information fraction ("IF") of the planned total number of 319 events. If the second IA is skipped, no alpha will be spent for the second IA and the remaining alpha level after the first IA will be used at the FA. The significance level for the PFS FA will be calculated according to the actual alpha(s) spent at IA(s). If less than 319 events are observed, the significance level will be based on the planned 319 events without further adjustment for the actual total number of PFS events.

Figure 10.1.1-1: PFS Assumptions of the CA209-8HW Study



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

PFS in 1L for comparison between arms B vs C

The sample size for the PFS B vs C in 1L is determined with following additional assumptions:

- The distribution of PFS in arm A in 1L is assumed based on observed data in the Keynote-177 study. Table 10.1.1-3 presents the assumed PFS rates for arm A in 1L and the PFS rates in arm B in 1L by assuming a constant HR of 0.6 vs arm A in lL.
- The distribution of PFS in arm C in 1L follows exponential distribution with median PFS of 9 months.

The assumed PFS curves of arms A, B and C in 1L is presented in Figure 10.1.1-1. Based on simulations, approximately 125 PFS events will provide about 99% power to detect an average HR of 0.55 with an overall type 1 error of 0.044 (two-sided). Under the assumption of a staggered enrollment, it is required to randomize approximately 230 1L participants to arms B and C during Part 1 and Part 2 enrollment at 2:1 ratio.

This design accounts for one PFS interim look when 85% of the total number of events are observed (approximately 106 events) and after the last participant is randomized during Part 2 enrollment. The final analysis is projected to be approximately 47 months, from the date of first participant being randomized to Part 1.

To ensure the sample size is sufficient for both of the primary endpoints as discussed above, Part 1 randomization will be closed when approximately 442 participants randomized with central lab confirmed dMMR/MSI-H. This translates to an approximate number of participants in arm A (N=190), B (N=190) and C (N=62) as arm C will only randomize participants who received 0 or 1 prior lines of therapy. Part 2 will randomize approximately 230 1L participants with central lab confirmed dMMR/MSI-H. This translates to an approximate number of participants in arm A (N=92), B (N=92) and C (N=46).

PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. Therefore, PFS B vs C in 1L is concluded and will not be tested again in a final analysis.

Table 10.1.1-3: PFS Rates and Hazard Ratio for 1L Participants

Period	Cumulative PFS rates for Nivolumab (Arm A) (%) in 1L	Cumulative PFS rates for Nivolumab + Ipilimumab (Arm B) (%) in 1L	Hazard Ratio of B vs A in 1L
0 - 1 month	93.0	95.7	0.6
3 months	67.0	78.6	0.6
6 months	55.0	69.9	0.6
9 months	52.0	67.5	0.6
12 months	50.0	66	0.6
18 months	47.0	63.6	0.6
24 months	45.0	61.9	0.6
30 months	42.0	59.4	0.6

Table 10.1.1-3: PFS Rates and Hazard Ratio for 1L Participants

Period	Cumulative PFS rates for Nivolumab (Arm A) (%) in 1L	Cumulative PFS rates for Nivolumab + Ipilimumab (Arm B) (%) in 1L	Hazard Ratio of B vs A in 1L
36 months	37.0	55.1	0.6
42 months and after	35.0	53.3	0.6

Abbreviations: PFS, progression free survival

10.1.2 Power Calculation of Secondary Endpoints

This section describes the power for the secondary endpoints of PFS of arms B vs A in 1L, ORR and OS comparisons between arms B vs A in all lines and ORR of arms B vs C in 1L and B vs A in 1L to be tested under the planned testing procedure (Section 10.3.10). Based on the planned testing procedure, there is no initial alpha allocation to these endpoints. These endpoints only will be tested once alpha from endpoint(s) at higher order meet the statistical significance at the pre-specified significance level at IA or FA.

PFS in 1L for comparison between arms B vs A

The PFS comparison between arm B vs arm A for 1L participants is the first secondary endpoint. Using the sample size as determined for the primary endpoints, the power calculation for PFS B vs A in 1L is calculated under the following assumptions:

- The PFS KM curve in arm A 1L follows the piece-wise exponential distribution as presented in Table 10.1.1-3 (Figure 10.1.1-1).
- A constant HR of 0.6 is assumed for PFS in 1L arm B vs arm A
- The concurrent randomization ratio of arm B vs arm A is 1:1 Based on the sample size determined by the primary endpoints, it is estimated that a total of 308 1L participants will be concurrently randomized to arms A and B
- One interim analysis of PFS of arm B vs arm A in 1L is planned. PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. If PFS B vs A in all lines meets its pre-specified statistical criteria at its first interim analysis with the data cut-off around Aug-2024, interim analysis of PFS B vs A in 1L will be conducted at the same time. It is projected that approximately 75% of the total number of PFS events of arm B vs arm A in 1L will be observed (approximately 117 events) in around Aug-2024. If PFS B vs A in all lines does not meet the pre-specified statistical criteria at its first interim analysis, PFS B vs A in 1L interim analysis will be skipped and the endpoint will be tested at its final analysis. Details on the testing procedure is described in Section 10.3.10.
- Under the above assumptions, a total of 156 PFS events will provide approximately 87% power with two-sided alpha of 0.044 to demonstrate statistical significance of arm B vs arm A in 1L. If PFS B vs A in all lines does not meet the pre-specified statistical criteria in the final analysis and PFS B vs A in 1L is tested with alpha of 0.02 passed only from PFS B vs C in 1L, 156 PFS events will provide approximately 79.5% power. Final analysis of PFS B vs A in 1L will be

conducted when approximately 156 events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first.

The secondary endpoints of ORR of arms B vs A in all lines, OS of arms B vs A in all lines, ORR of arms B vs C in 1L, ORR of B vs A in 1L, OS of arm B vs C in 1L and OS of arm B vs A in 1L will be tested under the planned testing procedure described in protocol Section 10.3.10. Based on the planned testing procedure, there is no initial alpha allocation to these endpoints. These endpoints will only be tested once alpha from endpoint(s) at higher order meets the statistical significance at the pre-specified significance level at IA or FA. The power of ORR and OS tests based on the assumption that all PFS tests meet the pre-specified statistical criteria at the interim or final analysis is listed below.

ORR in all lines for comparison between arms B vs A

ORR comparison between arm B vs arm A in all lines is a key secondary endpoint. The observed ORR per BICR assessment for all treated participants in study CA209142 are 54.6% and 36.5% for the combination and monotherapy arms, respectively (data on file, Aug 2018), resulting in the ORR difference of approximately 18%. Considering the approximately 564 randomized participants to arm A and arm B as determined by the primary endpoints of PFS, there will be about 93.1% power to show a statistically significant result in ORR between arm B and arm A with an overall type 1 error of 0.006 (two-sided). The ORR comparison between arm B vs arm A will be tested under the pre-specified testing procedure in order to control the overall type I error of the study (Section 10.3.10).

ORR in 1L for comparison between arms B vs C

ORR comparison between arm B vs arm C in 1L is a key secondary endpoint. The observed ORR per BICR assessment in the chemotherapy arm in the Keynote-177 study is 33% and the observed ORR per BICR assessment for 1L combination cohort is 62% (data on file, Nov 2019 DBL),[92] resulting in the ORR difference of approximately 29%. Considering the approximately 230 randomized participants to arm B and arm C as determined by the primary endpoints of PFS, there will be about 98% power to show a statistical significant result in ORR between arm B and arm C with an overall type 1 error of 0.044 (two-sided). The ORR comparison between arm B vs arm C in 1L will be tested under the pre-specified testing procedure in order to control the overall type I error of the study (Section 10.3.10).

ORR in 1L for comparison between arms B vs A

ORR comparison between arm B vs arm A in 1L is a key secondary endpoint. The observed ORR per BICR assessment in the pembrolizumab arm in the Keynote-177 study is 44% and the observed ORR per BICR assessment for 1L combination cohort is 62% (data on file, Nov 2019 DBL),[92] resulting in the ORR difference of approximately 18%. Considering the approximately 308 randomized participants to arm A and arm B as determine by the primary endpoints of PFS, there will be about 86% power to show a statistical significant result in ORR between arm B and arm A with an overall type 1 error of 0.044 (two-sided). The ORR comparison between arm B vs arm A

in 1L will be tested under the pre-specified testing procedure in order to control the overall type I error of the study (Section 10.3.10).

OS in all lines for comparison between arms B vs A

OS comparison between arm B vs arm A in all lines is a key secondary endpoint. The OS distribution is under similar assumptions as for PFS, ie, of a piecewise exponential distribution for OS KM curve in arm A and a constant HR of arm B compared to arm A.

Based on the observed OS curve and rates in the nivolumab monotherapy cohort of CA209142 from the November 2019 DBL (data on file), the OS distribution for nivolumab monotherapy arm was assumed to be piecewise exponential with the following landmark OS rates, as presented in Table 10.1.2-1 below:

Table 10.1.2-1: OS Rates and Hazard Ratios

Period	Cumulative OS Rate for Nivolumab (%)	Cumulative OS Rate for Nivolumab and Ipilimumab Combination (%)	Hazard Ratio
0 - 1 month	97.0	98.0	0.65
3 months	89.0	92.7	0.65
6 months	82.0	87.9	0.65
9 months	75.0	82.9	0.65
12 months	70.0	79.3	0.65
18 months	65.0	75.6	0.65
24 months	58.0	70.2	0.65
30 months	55.0	67.8	0.65
36 months	54.0	67.0	0.65
42 months and after	52.0	65.4	0.65

Abbreviations: OS, overall survival

Under this assumption of a constant HR and considering the approximately 564 randomized participants to arm A and arm B as determined by the primary endpoints of PFS, approximately 243 OS events provide about 91% power to detect a HR of 0.65 with an overall type 1 error of 0.05 (two-sided).

This calculation accounts for two OS interim looks planned: the first look is at the time of the PFS interim analyses and the second look is at the time of the PFS final analyses. The final OS analysis was initially planned at approximately 5 years after the randomization of the first participant, which is no longer feasible as explained in Section 10.1.1. To allow extended follow-up for survival data collection, final OS analyses will be conducted 3 years after the last participant from Part 2 enrollment was randomized ("3-year minimum follow-up"): the final analysis of OS B vs A in all lines will be conducted when approximately 243 events are observed or 3-year minimum

follow-up is achieved, whichever occurs first. OS event accumulation is expected to be very limited (eg, very few events per year) after 3-year minimum follow-up based on blinded OS event projections. Data from study CA209142 and from an external study of single agent checkpoint inhibitors in 1L MSI-H/dMMR mCRC for which long-term results are available illustrates flattening of OS Kaplan-Meier curves starting from Month 36.[91,93]

The OS will be tested under the pre-specified testing procedure (Section 10.3.10) in order to control the type I error.

10.2 Populations for Analyses

Corresponding with the two primary endpoints, the study will have two sets of participants for conducting statistical analyses. The populations defined below (except for enrolled participants) will apply to each of the sets of participants unless otherwise specified:

- All lines participants: all participants across lines randomized to arms A, B and C through Part 1 and Part 2 enrollment.
- 1L participants: all participants in 1L randomized to arms A, B and C through Part 1 and Part 2 enrollment.

For purposes of analyses, the following populations are defined:

Population	Description
Enrolled	All participants who signed an informed consent form and were registered into the IRT system.
Randomized	All participants who were randomized to any treatment arm in the study.
Confirmed dMMR/MSI-H	All randomized participants who have centrally confirmed dMMR/MSI-H status by either central test (IHC or PCR). This is the primary population for efficacy analyses.
Confirmed dMMR/MSI-H by IHC	All randomized participants who have centrally confirmed dMMR/MSI-H status by central test per IHC. This is the primary population for efficacy analyses supporting IVD of IHC.
Confirmed dMMR/MSI-H by PCR	All randomized participants who have centrally confirmed dMMR/MSI-H status by central test per PCR. This is the primary population for efficacy analyses supporting IVD of PCR.
Treated	All participants who received at least one dose of study treatment (nivolumab or ipilimumab or investigator's choice chemotherapy). This is the primary population for safety analyses.

Population	Description
Response Evaluable	All randomized participants who have baseline and at least one on-study evaluable tumor measurement. This population will be defined based on Investigator and BICR data.
PK	All treated participants with available serum time-concentration data.
Immunogenicity	All treated participants with available immunogenicity data.
Biomarker	All randomized participants with available biomarker data.
Outcomes Research	All randomized participants who have an assessment at baseline and at least one subsequent post-baseline assessment (for EORTC QLQ-C30, QLQ-CR29 and EQ-5D-3L separately).
Crossover Cohort treated	All participants who received at least one dose of study medication following crossover to the nivolumab plus ipilimumab treatment.

As appropriate, other populations will be defined in the Statistical Analysis Plan (SAP).

Participants enrolled in the China extension will not be included in the above listed populations for analyses.

10.3 Statistical Analyses

10.3.1 General Considerations

The primary and key secondary estimands are described in Table 4-1.

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary, secondary and other key endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

Analyses related to the China Sub-study which includes enrolled participants in China extension will be specified in the China-specific protocol and China-specific SAP.

10.3.2 Efficacy Analyses

The primary efficacy population will be the “Confirmed dMMR/MSI-H” participants. Appropriate analyses will be performed for “Confirmed dMMR/MSI-H by IHC” and “Confirmed dMMR/MSI-H by PCR” to demonstrate comparable efficacy based on dMMR/MSI-H by one of the central test. These analyses will support the clinical utility of the IVD for each of the central test. SAP will document further details. The endpoints defined below will apply to both All participants and 1L participants, unless otherwise specified.

Endpoint	Statistical Analysis Methods
Primary	
BICR-assessed Progression-free survival (PFS) is defined as the time from the randomization date to the date of first objectively documented disease progression per RECIST 1.1 (ie, radiologic) or death due to any cause, whichever occurs first. • Participants who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. • Participants who did not progress or die will be censored on the date of their last tumor assessment. • Participants who did not have any on study tumor assessments and did not die will be censored on the randomization date. • Participants who started any subsequent anti-cancer therapy without a prior reported progression or prior to death will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. • Further explanation for various censoring scenarios for PFS will be specified in SAP.	The distribution of PFS will be compared via a two-sided, log-rank test stratified by randomization stratification factors of line of therapy (not applicable to PFS in 1L) and tumor sidedness recorded in IRT at the allocated significance level at IA and FA. The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate, stratified by line of therapy and tumor sidedness as recorded in IRT. PFS curves will be estimated using Kaplan-Meier (KM) product-limit methodology. Median PFS with two-sided 95% confidence interval (CI) using the Brookmeyer and Crowley method (with log-log transformation) will be computed. In addition, PFS rates at a specific time point (eg, 6, 12, 24 months) with two-sided 95% CI using the log-log transformation will be computed.
Secondary	
Investigator-assessed PFS is defined similarly as BICR-assessed PFS.	Analyses methods for PFS by investigator will be similar as PFS by BICR.
Overall Survival (OS) is defined as the time from the randomization date to the date of death due to any cause. A participant who has not died will be censored at last known date alive.	Analyses methods for OS will be similar as PFS.

Endpoint	Statistical Analysis Methods
Best Overall Response (BOR) for a participant will be assessed per RECIST 1.1 by BICR and by investigator. BOR is defined as the best response designation, recorded between the randomization date and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of initiation of subsequent therapy, whichever occurs first. For participants without documented progression or initiation of subsequent therapy, all available response designations will contribute to the BOR determination. Objective Response Rate (ORR) is defined as the proportion of all randomized participants whose BOR is either confirmed complete response (CR) or confirmed partial response (PR). Disease Control Rate (DCR) is defined as the proportion of participants whose BOR is confirmed CR or confirmed PR or stable disease (SD) for at least 12 weeks. Time to Response (TTR) is defined as the time from the randomization date to the date of first confirmed CR or PR. TTR will be evaluated for responders only. Duration of Response (DOR) for a participant with a BOR of confirmed CR or PR, is defined as the time between the date of first confirmed response and the date of the first objectively documented tumor progression per RECIST 1.1 or death due to any cause, whichever occurs first. The rules of censoring are the same as PFS.	ORR will be compared using a two-sided stratified Cochran Mantel Haenszel (CMH) test using stratification as recorded in IRT. Associated odds ratio and estimate of the difference in ORRs with 95% CI will be calculated. The ORR/DCR will be summarized by binomial response rates and corresponding two-sided 95% exact CI using the Clopper-Pearson method. TTR will be summarized using the mean, median, minimum and maximum values, and standard deviation. Analyses methods for DOR will be similar as PFS/OS.

Endpoint	Statistical Analysis Methods
Exploratory	
Investigator-assessed second disease progression or death (PFS2) is defined as the time from randomization to the date of investigator-defined documented disease progression per RECIST 1.1 during next line of treatment or death due to any cause, whichever comes first. Clinical deterioration will not be considered as progression. Participants who were alive and without progression after the next line of therapy will be censored at last known alive date. Explanation for censoring of PFS2 will be specified in SAP.	Analyses methods for PFS2 by investigator will be similar as PFS/OS.
Investigator-assessed time to treatment failure (TTF) is defined as the time from randomization to the date of treatment discontinuation regardless of the cause. Participants who were on treatment will be censored at the last know alive date.	Analyses methods for TTF by Investigator assessment will be similar as PFS/OS.
Recurrence free survival (RFS) is defined as the time from the date of the on study curative surgery to the disease recurrence as assessed by investigator per RECIST 1.1 or death due to any cause, whichever occurs first. This will be evaluated for participants who receive on study curative surgery.	Analyses methods for RFS by Investigator assessment will be similar as PFS/OS.

10.3.3 Safety Analyses

All safety analyses will be performed on the Treated population. Below is a summary of planned statistical analyses of key safety endpoints. Additional analyses will be described in the SAP.

Endpoint	Statistical Analysis Methods
Exploratory	
Incidence of AEs, SAEs, AEs leading to discontinuation (with or without relationship to study drug), and deaths AEs will be graded according to CTCAE (Version 5).	AEs will be summarized using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT. Deaths will be summarized using frequency distribution.

Endpoint	Statistical Analysis Methods
Laboratory abnormalities Laboratory values will be graded according to NCI CTCAE (Version 5)	Laboratory abnormalities will be summarized using the worst CTC grade on treatment per participant

10.3.4 Analyses of Crossover Cohort Treated Participants

As discussed in Section 5.1 participants in arm C who have BICR-confirmed PD on or following Investigator's Choice chemotherapy have the option to receive nivolumab plus ipilimumab combination therapy.

Impact of crossover in arm C to the key efficacy and safety endpoints:

As crossover occurs after the BICR confirmed disease progression and completion of follow-up visit 1, it will not impact the tumor based efficacy endpoint such as PFS, ORR, DOR and DCR. For the OS analyses, intention to treat principle will be followed, i.e., regardless of crossover status of participants in the arm C. It should not impact safety analyses as crossover occurs after completion of follow-up visit 1. However, for rare situations such as an adverse event lasts beyond the first follow-up visit, or the IMAE analyses which uses 100 days window from last dose date (although it is unlikely to see IMAE in arm C), safety analysis will include all events occur upon initiation of crossover.

Analyses of Crossover Cohort:

The same methodologies as used for the primary, secondary and exploratory efficacy endpoints will be used to analyze any specific endpoints defined to evaluate the clinical activity of the nivolumab plus ipilimumab combination treatment after crossover, if feasible.

Selected safety analyses will be repeated to evaluate the safety of the combination treatment after crossover.

Other analyses including pharmacokinetic, immunogenicity, biomarker and outcome research will be conducted as described in respective sections of the protocol, if feasible. Details on the analysis of the crossover-treated participants will be defined in the SAP.

10.3.5 Pharmacokinetic Analyses

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

10.3.6 Immunogenicity

Summary of the incidence of ADA-positive status (such as persistent positive, only last sample positive, other positive, baseline positive) and ADA-negative status relative to baseline will be reported. In addition, presence of neutralizing antibodies may be reported, if applicable. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

10.3.7 Biomarker Analyses

Summary measures of change (or % change) from baseline in various biomarkers and summary measures of anti-tumor activity by pretreatment level of biomarkers of interest will be provided. Methodology for exploratory biomarker analyses will be further described in the SAP.

10.3.8 Outcomes Research Analyses

10.3.8.1 EORTC QLQ-C30 and QLQ-CR29

The analysis of EORTC QLQ-C30 and QLQ-CR29 will be performed in all randomized participants who have an assessment at baseline and at least one subsequent assessment. The questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms. Baseline, each post baseline assessment, and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 and QLQ-CR29 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean with SC and 95% CI, median, first and third quartiles, minimum, maximum). In addition, the percentage of participants demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number participants assessed at assessment time point.

10.3.8.2 EQ-5D-3L

Participant's overall health state on a visual analog scale (EQ-VAS) and utility index scores (based on UK weighting algorithm[94]), at each assessment time point will be summarized using descriptive statistics (N, mean, with SD and 95% CI, median, first and third quartiles, minimum, maximum). The proportion of participants reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D-3L dimensions at each assessment time point. Percentages will be based on number participants assessed at assessment time point.

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

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

10.3.9 Other Analyses

Data on PFS, OS, ORR, and BOR will be summarized for randomized participants with dMMR/MSI-H confirmation per each in vitro diagnostic (IVD)/companion diagnostics (CDx) testing methodology.

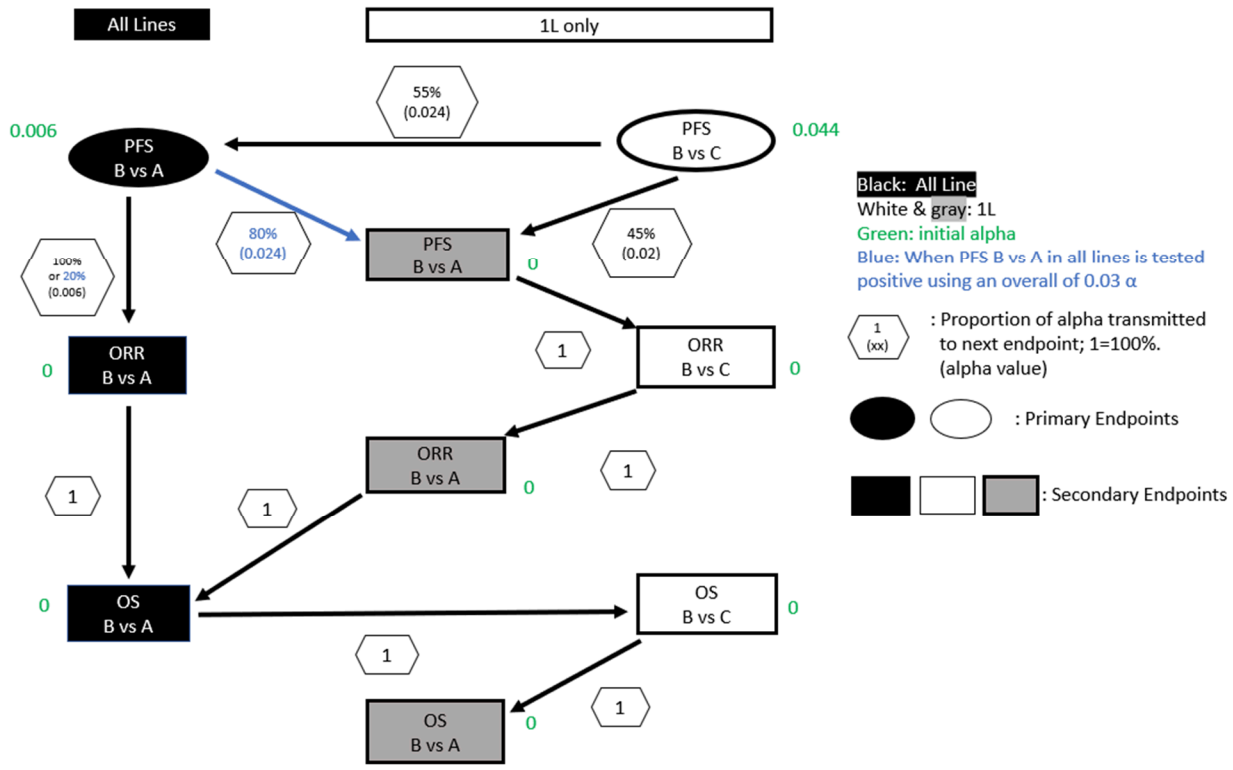
10.3.10 Strong Control of Type I Error

The following testing strategy provides a strong control of family wise error rate (FWER) at alpha (α) level of 5% for the primary and key secondary endpoints of this study.

For the 2 primary endpoints of PFS B vs A in all lines and PFS B vs C in 1L, 0.6% and 4.4% are initially allocated respectively. The interim analysis (IA) of each primary PFS will be event driven. If the projection suggests that IA of PFS B vs A in all lines and IA of PFS B vs C 1L will occur within 3 months from each other, they can be combined and conducted at the latest projected time. Details are defined in Section 10.3.11. Figure 10.3.10-1 presents the graphical approach to be used to control the type I error in a strong sense for testing of primary and key secondary endpoints.[95] For example, if PFS B vs C in 1L meets the pre-specified statistical criteria at the interim or final analysis, then 2.4% α will be passed to PFS B vs A in all lines and 2% α will be passed to PFS B vs A in 1L. PFS B vs A in all lines will then be tested with 3% α (0.6% initial α plus 2.4% α passed from PFS B vs C in 1L). If PFS B vs A in all lines meets the pre-specified statistical criteria at the interim or final analysis, then 2.4% α will be passed to PFS B vs A in 1L, and PFS B vs A in 1L will be tested with a total of 4.4% α. If PFS B vs A in all lines does not meet the pre-specified statistical criteria at the final analysis, then PFS B vs A in 1L will be tested with 2% α which is collected from PFS B vs C in 1L only.

The testing procedure will only allow to test a secondary endpoint if all the precedent endpoints complete their tests. Testing will only be performed in the forwarding path (no retrospectively testing) and if an endpoint receives alpha from two precedent endpoints, the endpoint will only be tested once the testing of these two endpoints are completed (regardless of significance or not). Full scope of statistical testing procedure will be documented in the SAP, including additional secondary endpoints of OS to be tested and details of alpha spending at IA and FA for each endpoint.

Figure 10.3.10-1: Testing Procedure for Primary and Secondary Endpoints



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

10.3.11 Interim Analyses

The DMC will be utilized to provide an independent evaluation of the study interim data. An independent statistical group will be utilized to conduct unblinded monitoring of pooled events of the two corresponding arms of each comparison in order to track the number of events by each comparison.

Study-wise, there are two interim analyses (IA) planned for primary and secondary endpoints prior to the final analysis of OS endpoints.

- The first interim analysis of the study is planned for the interim analysis for both the primary endpoints of PFS. Considering the variability of the enrollment assumptions from the actual enrollment rate and differences of the shape of PFS curves in arms A, B, and C, this study plans to have the interim analysis of PFS for the 2 primary endpoints at the same time when the latest of the targeted number of events of each endpoint is observed and after the last participant is randomized during Part 2 enrollment. In other words, the first interim analysis of the study was planned to be triggered when at least 85% of the total number of events were observed for both PFS primary endpoints and after the last participant was randomized during

Part 2 enrollment. Separate database locks for IA PFS B vs C in 1L and IA PFS B vs A in all lines may be conducted if the locks are expected to occur at least 3 months apart from each other. As of Protocol Amendment 10, PFS B vs C in 1L has been tested at its interim analysis (Data cut-off date: 12-Oct-2023; DBL: 15-Nov-2023) and met the pre-specified statistical criteria. Interim analysis of PFS B vs A in all lines will be conducted in a separate DBL with a data cut-off in around Aug-2024 ("PFS B vs A all lines IA1 DBL"). If PFS B vs A in all lines does not meet the pre-specified statistical criteria in the first interim look, a second interim look ("PFS B vs A all lines IA2 DBL") may be conducted if the projected time between the second interim look and final look is more than 6 months. The interim analysis of the secondary endpoint PFS B vs A in 1L will be conducted when PFS B vs A in all lines meets the pre-specified statistical criteria at its interim analysis. The stopping boundaries at the interim analysis for each of the PFS endpoints will be derived based on the exact number of events observed in the locked database using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. For any PFS endpoint, if the timing of interim analysis based on this trigger is too close to the projected time of its final analysis (eg, within 6 months), the interim analysis of this specific PFS endpoint may be skipped and the endpoint will be tested at the final analysis.

- Since PFS B vs C in 1L has been concluded, the second interim analysis of the study will be the final analysis of PFS B vs A in all lines and PFS B vs A in 1L, which will be conducted when the required number of total events are observed or 2 years after the last participant from Part 2 enrollment was randomized, whichever occurs first.
- The final analysis of this study will include the final OS analysis for arm B vs arm A in all lines, Arm B vs Arm C in 1L, and Arm B vs Arm A in 1L, which will be conducted 3 years after the last participant in Part 2 enrollment was randomized.
- As described above, these interim and final analyses may be triggered by more than one endpoints and therefore all the events observed in the two arms for the corresponding comparisons will be used for the analyses. For a given endpoint, the stopping boundaries (alpha allocation) at interim analysis will be derived based on the exact number of events observed in the locked database (vs target number of events at final analysis) using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. In the scenario that the final analysis of an endpoint is events-driven and the locked database has more events than planned, the final allocation of alpha will be adjusted based on actual number of events observed at the final analysis.

Additional secondary endpoints will be tested per the testing procedure (Section 10.3.10) at these interim and final analyses. Once one of the primary endpoints of PFS meets the pre-specified statistical criteria at the interim or final analyses, the secondary and exploratory endpoints in the same set of participants will be analyzed. Secondary endpoints (to be tested under the testing procedure, Section 10.3.10) which have not met the pre-specified statistical significance level may not be reported in an aggregated fashion and may be analyzed at the final analysis.

In addition, an ad hoc interim analysis of ORR estimation in arm A, B and arm C for 1L participants may be conducted to support potential 1L regulatory submission's need. No statistical comparison

will be made among arms. Should such an interim analysis occur, the SAP will specify the details, including the timing, and number of participants to be used, prior to the database lock.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
2L	Second-line
5-FU	5-fluorouracil
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APCs	antigen-presenting cells
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CA19-9	cancer antigen 19-9
CBC	complete blood count
CDx	companion diagnostics
CEA	carcino embryonic antigen
CFR	Code of Federal Regulations
cHL	Classical Hodgkin's Lymphoma
CI	confidence interval
Cl	Chloride
CL	Clearance
CLcr	creatinine clearance
CMH	Cochran Mantel Haenszel

Term	Definition
CMS	consensus molecular subtype
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form, paper or electronic
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTC	circulating tumor cell
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
D	Day
DBL	database lock
DCR	disease control rate
DC/D	discontinuation/death
DILI	drug induced liver injury
dL	Deciliter
DLT	dose-limiting toxicity
DMC	data monitoring committee
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Term	Definition
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	EuroQol Group 5D-3L questionnaire
ESMO	European Society for Medical Oncology
FA	final analysis
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
FU	follow up
FWER	family wise error rate
g	Gram
GBS	Guillain-Barre syndrome
GCP	good clinical practice
GEP	gene-expression profiling
GFR	glomerular filtration rate
h	Hour
H&E	haemotoxylin and eosin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator brochure

Term	Definition
I-O	immuno-oncology
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ICOS	inducible T-cell costimulator
ID	infectious disease
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IHC	immunohistochemistry
IL	Interleukin
IMAE	immune-mediated adverse event
IMP	investigational medicinal products
INCa/HAS	Institut National du Cancer/Haute Authorite de Sante
IND	Investigational New Drug application
INR	international normalized ratio
IP	investigational product
Ipi	Ipilimumab
IRB	Institutional Review Board
Irino	Irinotecan
IRT	interactive response system
IU	International Unit
IV	Intravenous
IVD	in vitro diagnostic device
K+	Potassium
KM	Kaplan Meier
L	Liter
LDH	lactate dehydrogenase
LFT	liver function tests
mCRC	metastatic colorectal cancer
mOS	median overall survival
mPFS	median progression-free survival

Term	Definition
mTTR	median time-to-response
MDSC	myeloid-derived suppressor cell
mg	Milligram
MG	myasthenia gravis
Mg++	Magnesium
min	Minute
mL	Milliliter
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
MMR	mismatch repair (of DNA)
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability high
MSS	microsatellite stable
MTD	maximum tolerated dose
mWHO	modified World Health Organization
µg	Microgram
N	number of subjects or observations
Na+	Sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	non-evaluable
NGS	next generation sequencing
Non-IP	non-investigational product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction

Term	Definition
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PET	positron Emission Tomography
PFS	progression-free survival
PFS2	progression-free survival from next line of treatment (time to second progression)
PK	pharmacokinetics
PBMC	peripheral blood mononuclear cells
pMMR	proficient mismatch repair (of DNA)
PMR	post-marketing requirement
PO	per os (by mouth route of administration)
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PT	prothrombin time/preferred term
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QC	quality control
QD, qd	quaque die, once daily
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RFS	recurrence free survival

Term	Definition
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	squamous cell lung cancer
SD	stable disease
SJS	Stevens-Johnson syndrome
SOC	system organ class
SOP	standard operating procedures
Subj	subject
SUSAR	suspected, unexpected serious adverse reaction
t	temperature
T	time
TAS-102	trifluridine/tipiracil
T. bili	total bilirubin
TCR	T-cell receptor
TEN	toxic epidermal necrolysis
TMB	tumor mutational burden
TRAE	treatment related adverse event
TTD	time to treatment discontinuation
TTF	time to treatment failure
TTR	time to response
TSH	thyroid stimulating hormone
TSST	time to subsequent therapy or death
ULN	upper limit of normal
UC	urothelial carcinoma
US	United States of America
UV	ultraviolet

Term	Definition
VAS	visual analog scale
VEGF	vascular endothelial growth factor
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Regulation 536/2014
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered

electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from	The investigator or designee accepts responsibility for documenting traceability and

If	Then
the sites stock or commercial supply, or a specialty pharmacy)	study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

	If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

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

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

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.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

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

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

- Involvement in trial design.
- Participant recruitment (eg, among the top quartile of enrollers)

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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 User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (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 of WOCBP participant – Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. • Vasectomized **participant** assigned to receive chemotherapy – Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants

have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including, but not limited to, calendar, symptothermal, 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 treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] 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)

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 6 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 6 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 6 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 6 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

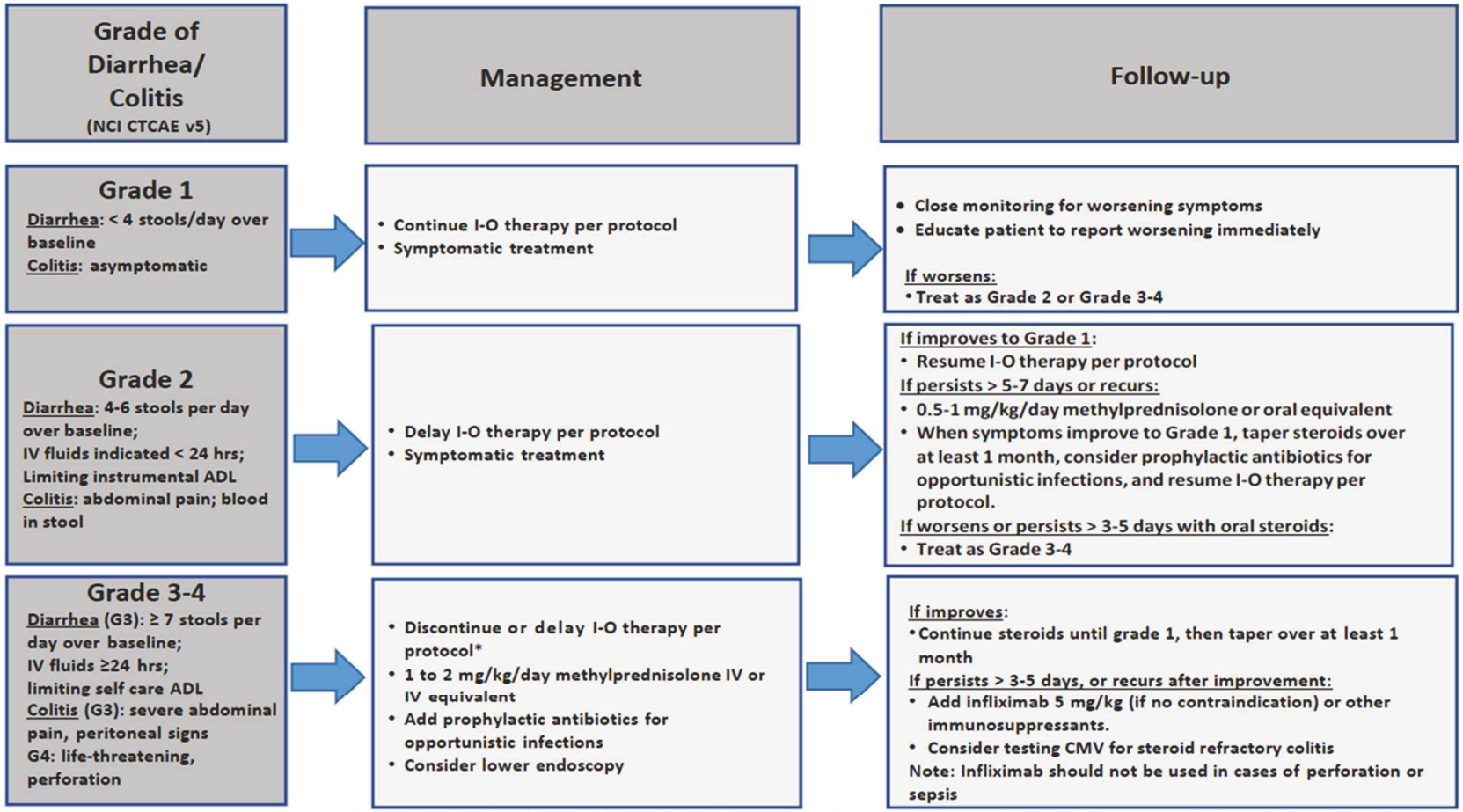
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



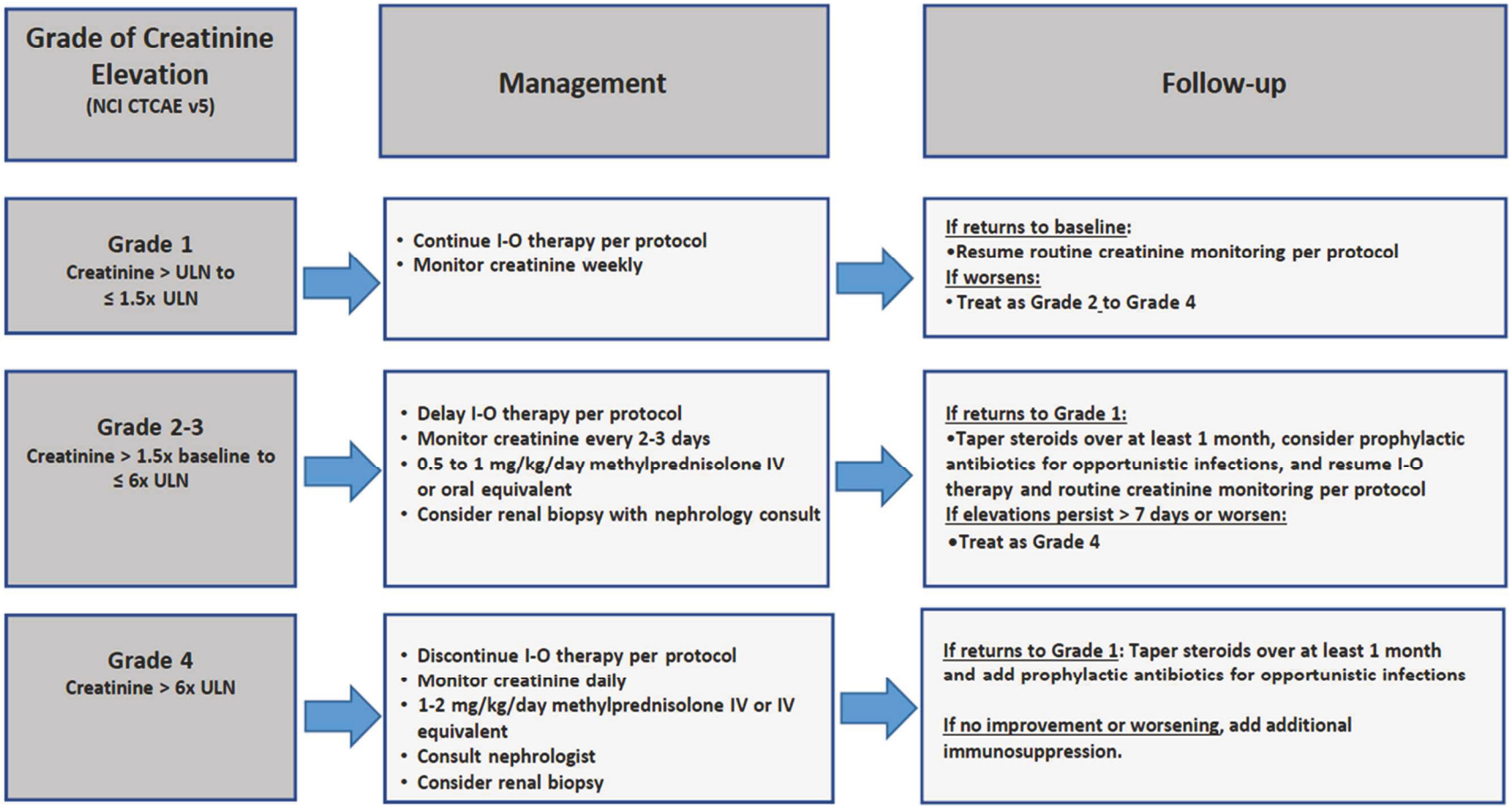
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

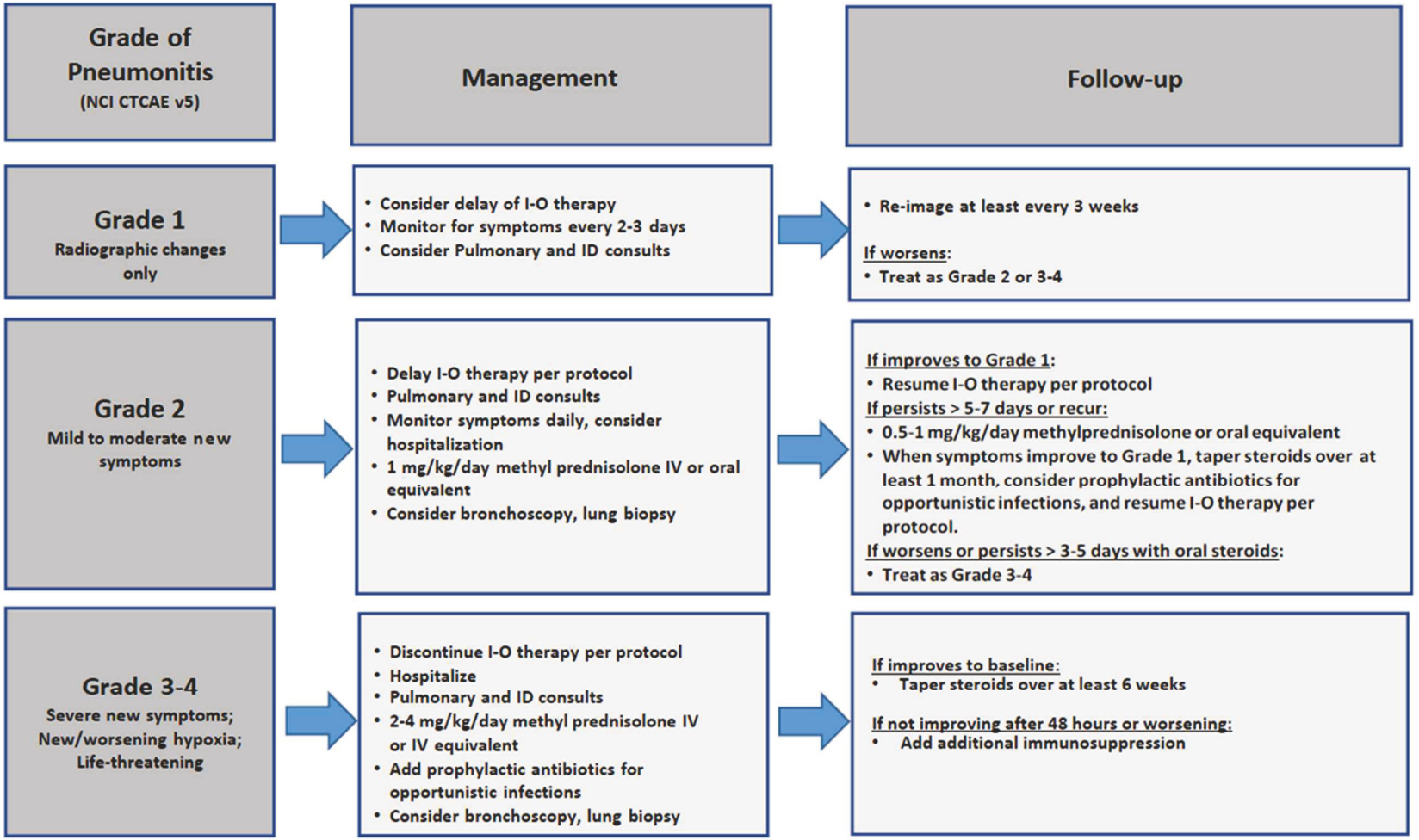


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

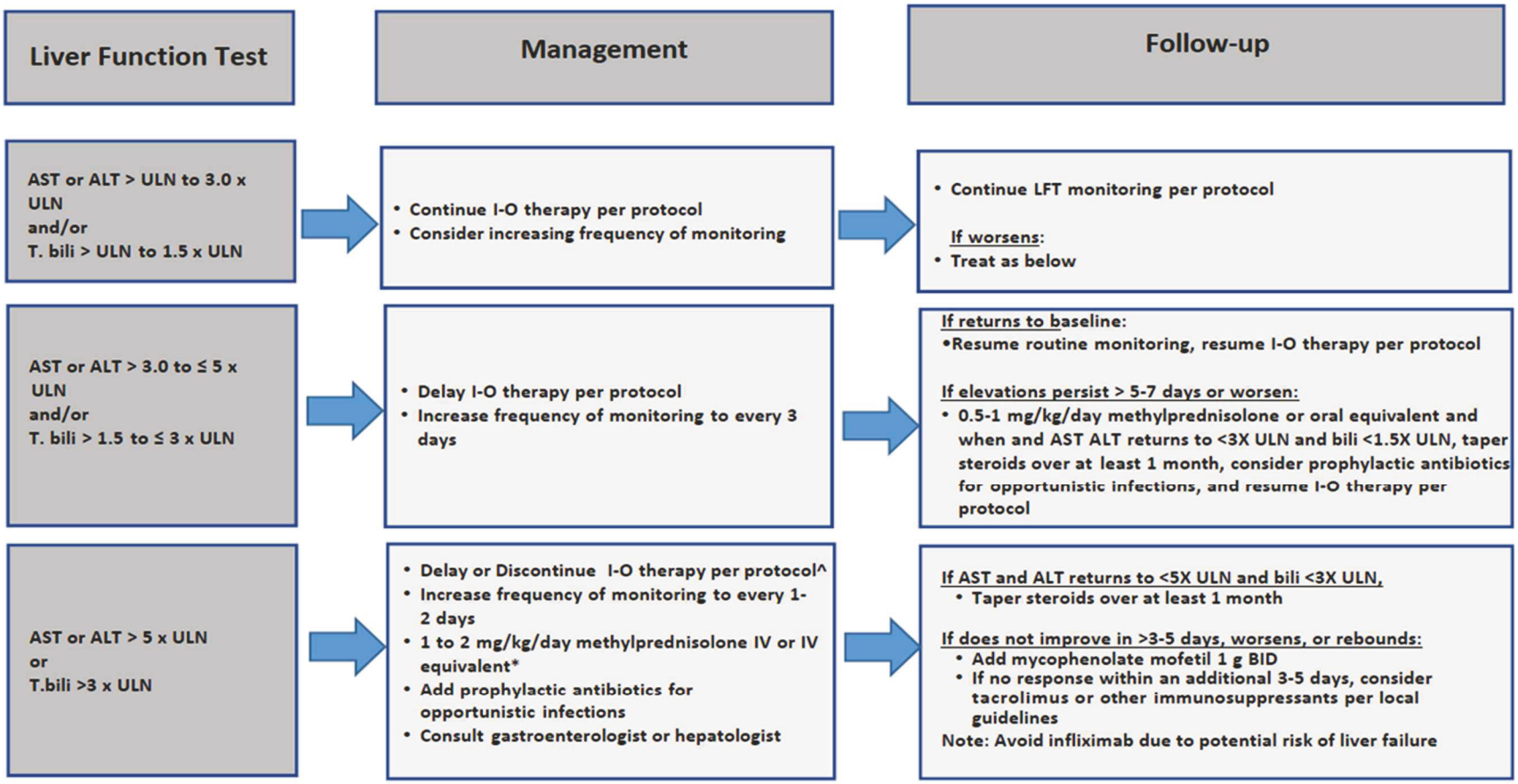


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

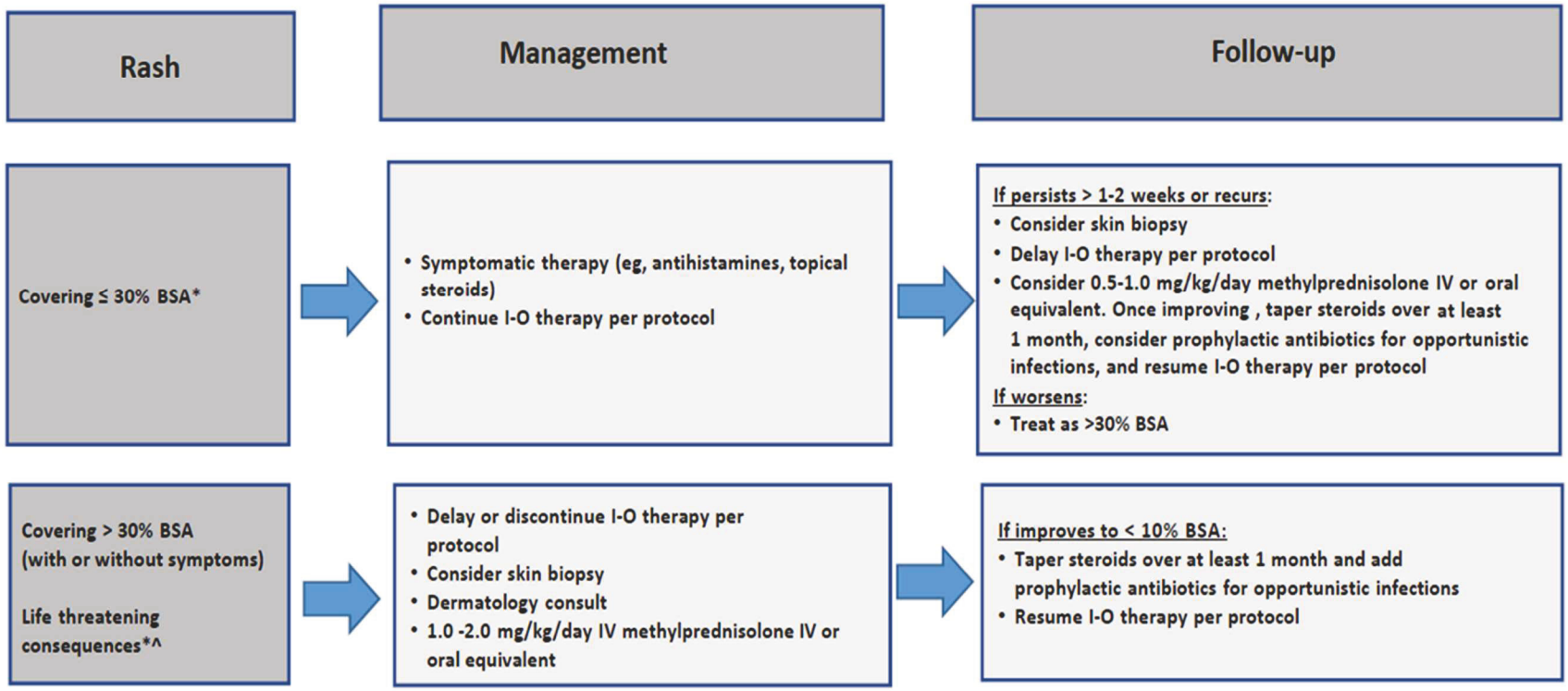
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

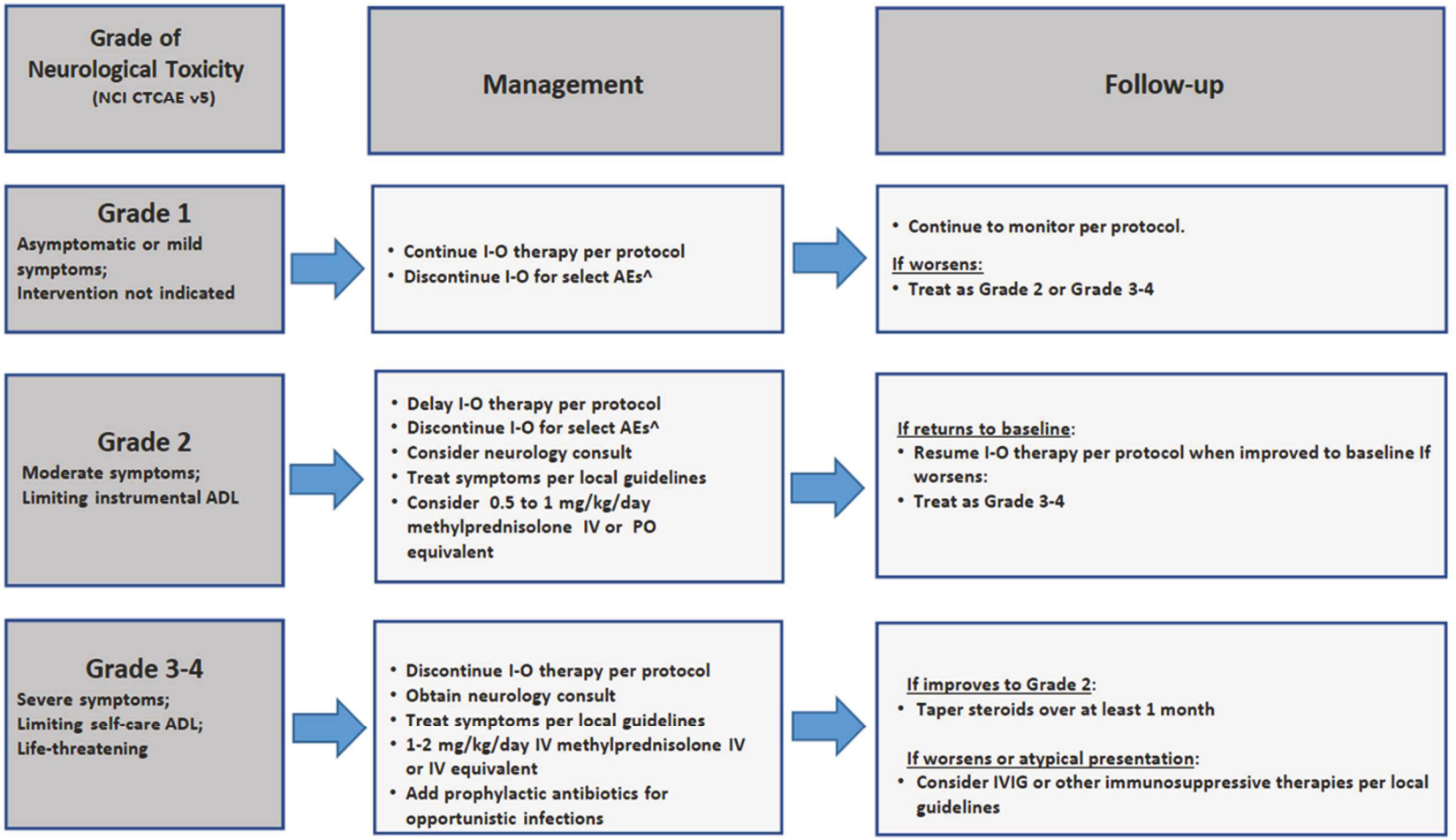
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



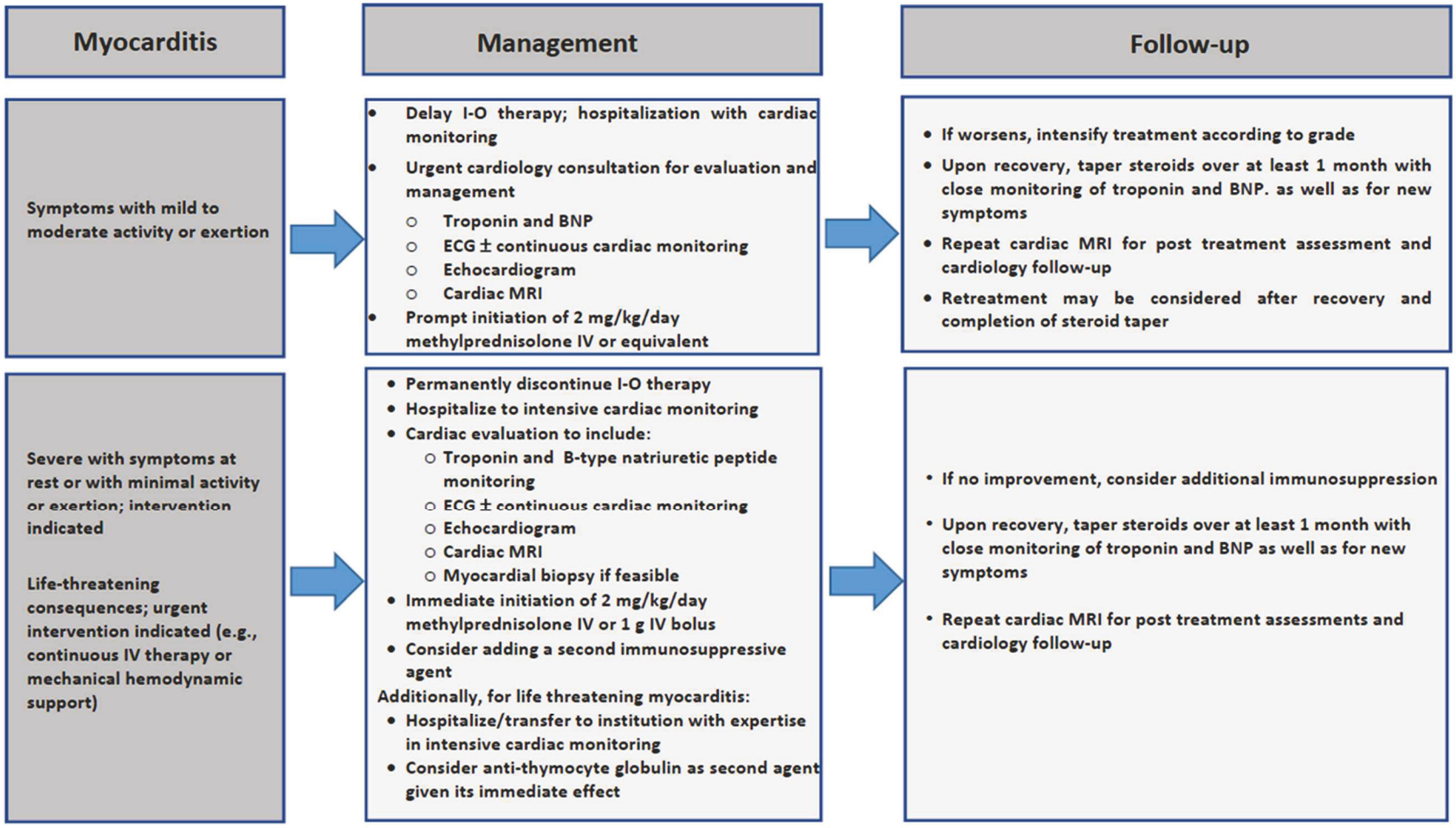
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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



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

28-Sep-2020

APPENDIX 6 ECOG PERFORMANCE STATUS

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the

patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

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

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

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 8 MSI STATUS TESTING

TESTING PANEL DESCRIPTIONS (PCR, IHC and Next Generation Sequencing [NGS])

FDA or other health authority approved testing should be used. If not, documentation demonstrating validation of the test performance (preferable under CLIA or equivalent ex-US) should be submitted for sponsor or representative to review.

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

- Reference panel:
  - BAT25 (mononucleotide)
  - BAT26 (mononucleotide)
  - NR-21 (mononucleotide)
  - NR-24 (mononucleotide)
  - MONO-27 (mononucleotide)
  - D5S346 (dinucleotide)
  - D2S123 (dinucleotide)
  - D17S250 (dinucleotide)
- Alternative loci:
  - BAT40
  - BAT34C4
  - NR-22
  - TGF-β-RII
  - ACTC (635/636
  - CAT25
  - D9S63
  - D1S158
  - ACVR2A
  - BTBD7
  - DIDO1
  - MRE11
  - RYR3
  - SEC31A
  - SULF2
  -
- 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**

Promega MSI Multiplex system version 1.1

- 5 mononucleotide markers:
  - BAT-25
  - BAT-26
  - NR-21
  - NR-24
  - MONO-27
- Two polymorphic pentanucleotide markers
  - Penta C
  - Penta D
- Data interpretation:
  - MSS: no instability at any of the loci
  - MSI-Low: instability at a single mononucleotide locus
  - MSI-H: instability at ≥ 2 monoucleotide loci

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

Next generation sequencing methods:

- FoundationOne CDx
- FoundationOne Liquid CDx
- TSO500 Assay (Tissue)
- TSO500 ctDNA Assay
- PGDx Elio Plasma
- PGDx Elio Tissue
- Predicine ATLAS
- Personalis ImmunoID NeXT
- Tempus xT
- Caris Molecular Intelligence
- Oncomine Comprehensive Assay

- OmnisSeq MSI NGS
- QIAseq Tumor Mutational Burden Panels
- Guardant 360
- Guardant Omni
- Whole exome sequencing (Please record vendor, library kit, sequencing platform, read length, and read depth in eCRF if available)
- Whole genome sequencing (Please record vendor, library kit, sequencing platform, read length, and read depth in eCRF if available)
- Other, please record assay, platform and other details specified in eCRF

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 9 COUNTRY SPECIFIC APPENDIX

Criteria for exclusion of HIV-positive participants in Argentina, Czech Republic, Germany, and any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated.

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

Additional information on systematic screening for DPD deficiency added per Institut National du Cancer/Haute Authorite de Sante (INCa/HAS) recommendations in France and any Other Countries Where Screening is Locally Mandated.

Section Number & Title	Country-specific language
Section 6.2 Exclusion Criteria, 2), o	Added verbiage in bold: o) Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency**.** **If locally required a systematic screening for DPD deficiency has to be performed during study screening period, in compliance with INCa/HAS/local recommendations. In the case of total deficiency of DPD, defined based on local standards or as blood uracil level ≥ 150 ng/mL, the participant should be excluded from the study. If testing for DPD-deficiency was done prior to study entry and the medical documentation is available there is no need to repeat testing.**

Pregnancy added as a reason for permanent discontinuation from study treatment in Czech Republic and any Other Countries Where Locally Mandated

Section Number & Title	Country-specific language
Section 8.1 Discontinuation from Study Treatment	"In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In all cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy."
Section 9.2.5 Pregnancy	The following language is not applicable for the Czech Republic: "If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the

Section Number & Title	Country-specific language
	investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable."

Requirement added to perform additional endocrine tests (e.g. ACTH, cortisol) at screening and if clinically indicated while on treatment/FU in Japan and any Other Countries Where Locally Mandated

Section Number & Title	Country-specific language
Section 2 Schedule of Activities, Table 2-2: On Treatment Procedural Outline (CA2098HW) Arm A (Nivolumab Monotherapy) and Table 2-3: On Treatment Procedural Outline (CA2098HW) Arm B (Nivolumab + Ipilimumab Combination) Endocrine function testing	Added language on additional endocrine testing if clinically indicated. **Additional tests (e.g. ACTH, cortisol, etc.) should be performed during treatment phase if clinically indicated.** See Section 9.4.4
Section 2 Schedule of Activities, Table 2-5: Follow up assessments (CA2098HW) Endocrine function	Added language on additional endocrine testing if clinically indicated for participants who received nivolumab without or with ipilimumab. **Thyroid function testing should be done. Additional tests (e.g. ACTH, cortisol, etc.) should be performed if clinically indicated.**
Section 2 Schedule of Activities, Table 2-6: On Study (Baseline and on Treatment) Procedural Outline (CA2098HW) Optional Crossover Cohort Endocrine function testing	Baseline visit: Testing must be performed within 14 days prior to vial assignment. See Section 9.4.4 On-treatment visits: Thyroid function testing should be done every 6 weeks for the first 24 weeks, and then every 8 weeks until completion of study treatment. **Additional tests (e.g. ACTH, cortisol, etc.) should be performed during the treatment phase if clinically indicated.** See Section 9.4.4

APPENDIX 10 DEFINITION OF LINE OF THERAPY IN CA2098HW STUDY

In this study the number of prior systemic treatments for metastatic disease (line of therapy) will be used for stratification and treatment assignment purposes. Therefore proper identification of line of therapy is of critical importance.

The line of therapy refers to various chemotherapy treatments without or with anti-VEGF or anti-EGFR agent, that are given between diagnosis and each progression/recurrence.

The "line" changes when the patient progresses/recurs. Each line of therapy must be separated by a progression/recurrence date. Patients may have multiple regimens in each line if change of the regimen occured for reasons other than disease progression.

Some examples of the first and second-line settings provided below for your reference. Please note, that patients who progressed on or after triplet chemotherapy (FOLFOXIRI) without or with anti-VEGF or anti-EGFR agent, will be considered as if they have received two prior lines of systemic therapy.

No prior systemic treatment for metastatic disease = First-line therapy

- no prior systemic treatment in metastatic setting
- if patient received neoadjuvant/adjuvant therapy, then this therapy should be completed more than 6 months (> 6 months) before the diagnosis of metastatic or recurrent disease is made

One prior line of systemic treatment for metastatic disease = Second-line therapy

- patient received one prior line of systemic therapy in metastatic setting and experienced progression
- patient received neoadjuvant/adjuvant therapy and experienced recurrence within 6 months (≤ 6 months) after completion of therapy

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 09, 01-Jun-2023

Given the heterogeneity of patient populations (first-line [1L] and all lines) and different mode of action of study drugs (chemotherapy and immuno-oncology [I-O] therapy) the progression-free survival (PFS) event accumulation may not align for the 2 primary endpoints (PFS Arm B vs Arm C 1L and PFS Arm B vs Arm A all lines). The protocol is being amended to allow the option to trigger the interim analysis (IA) for each primary endpoint independently if the projected number of PFS events do not occur in close proximity to each other. In this case, separate database locks (DBLs) may be conducted for IA of each primary endpoint.

The protocol synopsis was updated to reflect changes in the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.10: Strong Control of Type I Error	Updated language about the timing of the interim analyses of the primary endpoints.	To align with Section 10.3.11 language update.
Section 10.3.11: Interim Analyses	Added a sentence to allow for flexibility to conduct separate database locks (DBLs), when the two primary endpoint interim analyses are projected to occur more than 3 months apart.	To allow the option to trigger the interim analysis for each primary endpoint independently in case that projected number of progression-free survival (PFS) events do not occur in close proximity to each other.
Appendix 8: MSI Status Testing	10 new markers/classifications were added.	Due to evolving testing methods per local standards, additional markers for local microsatellite instability (MSI) polymerase chain reaction (PCR) testing were added.
All	Minor edits and administrative changes.	To provide minor corrections and clarifications throughout the document.

Overall Rationale for Protocol Amendment 08, 04-Aug-2022

The purpose of this amendment is to specify that the data monitoring committee (DMC) will be utilized for the assessment of the study interim data and it will be providing recommendation to Bristol-Myers Squibb (BMS) on the next steps with regards to the study conduct.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Synopsis	Changes below as applicable.	To align with protocol body.
Section 5.1: Overall Design	Updated language in study design. Updated participant numbers under Figure 5.1-1 Study Schematic notes.	To provide a justification for the revision of the discordance rate between central and local dMMR/MSI-H testing results.
Section 5.1.1.1: Data Monitoring Committee	Added statement on DMC.	To implement an independent assessment of study interim data, without unblinding the sponsor.
Section 7.3: Blinding	Revised language about purpose of unblinding to the independent external statistical group.	For clarification given that the DMC, instead of the independent external statistical group, will conduct the evaluation of the study interim data.
Section 10.3.1: General Considerations	Removed the version number of the China-specific protocol.	To avoid referencing an outdated version of the China-specific protocol.
Section 10.3.11: Interim Analyses	Revised language about purpose of unblinding to the independent external statistical group. Added language on DMC.	For clarification given that the DMC, instead of the independent external statistical group, will conduct the evaluation of the study interim data.
Appendix 12: Guidance to Sites on Tumor Location and Sidedness	Added sidedness assignment for tumors located in rectum and rectosigmoid junction.	To clarify the tumor sidedness assignment.

Overall Rationale for Protocol Amendment 07, 10-May-2022

The main objective of Protocol Amendment 07 was to update the statistical analyses schedule to reflect new enrollment timelines for Part 2. In addition, the projection of the number of randomized participants based on local mismatch repair deficient/microsatellite instability high (dMMR/MSI-H) status has been revised to reflect higher than initially assumed discordance rate between central and local dMMR/MSI-H testing results. Other changes made to comply with Health Authorities' requests to include additional safety language around oxaliplatin use and clarification on contraception requirements for study participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Synopsis	Incorporated changes below, as applicable.	To align the synopsis with updated protocol language.
Table 4-1: Main Estimands for the Primary and Key Secondary Endpoints	Added clarifying language in main estimands for primary and key secondary endpoints.	For clarity
Section 5.1: Overall Design	Updated language in study design. Updated participant numbers under Figure 5.1-1 Study Schematic notes.	To provide a justification for the revision of the discordance rate between central and local dMMR/MSI-H testing results.
Section 5.2: Number of Participants	Updated projected number of randomized participants based on local dMMR/MSI-H status.	To reflect higher than initially assumed discordance rate between central and local dMMR/MSI-H testing results.
Section 6.1: Inclusion Criteria	Added clarifying language surrounding pregnancy prevention and added a sentence requiring women of childbearing potential (WOCBP) to use highly effective methods of contraception (failure rate < 1%).	To include additional language on pregnancy prevention requirements from Appendix 4 to the body of protocol to comply with health authority request and to updated to align with Bristol-Myers Squibb Company (BMS) internal guidance.
Section- 6.3: Optional Crossover for Participants treated in the Arm C	Added clarifying language surrounding pregnancy prevention and added a sentence requiring WOCBP to use highly effective methods of contraception (failure rate < 1%).	To include additional language on pregnancy prevention requirements from Appendix 4 to the body of protocol to comply with health authority request and to updated to align with BMS internal guidance.
Section 7.7.1: Prohibited and/or Restricted Treatments	Added statement about avoiding medicinal products that may prolong QT interval.	Incorporated language to global protocol to comply with health authority request.
Section 9.1.1: Imaging Assessment for the Study	Added language regarding the potential need for additional imaging acquisitions before	Additional clarifying language to facilitate transitioning to a fixed

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	transitioning to the every 16-week scan schedule.	schedule of tumor assessments from 8 to 16 weeks.
Section 9.1.1.2: BICR Assessment of Progression	Added language clarifying which scans should be used for crossover baseline scans.	Clarification for sites.
Section 9.4: Safety	Added language surrounding QT prolongation.	Incorporated language to global protocol to comply with health authority request.
Section 9.4.3: Electrocardiograms	Added additional language surrounding participant electrocardiogram monitoring.	Incorporated language to global protocol to comply with health authority request.
Section 9.8.1: Tissue Biomarkers	Added additional language regarding deoxyribonucleic acid (DNA)/ribonucleic acid (RNA) analysis from collected tumor tissue using sequencing techniques	Provide more clarity that sequencing techniques could be used.
Section 9.8.3.2: Whole Blood for Germline DNA	Added additional language that sequencing techniques such as whole exome sequencing can be used for whole blood DNA analysis	Provide more clarity that sequencing techniques could be used.
Section 9.8.3.4: Circulating Tumor DNA Analysis (Plasma) Biomarkers	Added additional detail on circulating tumor DNA (ctDNA) and that sequencing techniques can be used for ctDNA analysis.	Provide more clarity on ctDNA analysis and that sequencing techniques could be used.
Section 10.1: Sample Size Determination	Added clarification language regarding participants and clinical outcomes referred in sample size determination.	Added for clarification.
Section 10.1.1: Sample Size Determination of Primary Endpoints	Updated language under the Updated assumptions section.	Described the updated and streamlined statistical analyses schedule due to the new enrollment timelines for part 2.
Section 10.1.2: Power Calculation of Secondary Endpoints	Updated language related to timing of the interim analysis.	Described the updated and streamlined statistical analyses schedule due to new enrollment timelines for part 2.
Section 10.3.1: General Considerations	Re-arranged text and language.	For clarity.
Section 10.3.2: Efficacy Analyses	Added clarification language related to objective response rate (ORR) to secondary endpoint statistical analysis methods.	For clarity.
Section 10.3.4: Analyses of Crossover Cohort Treated Participants	Added clarification language related to crossover phase.	For clarity.
Section 10.3.11: Interim Analyses	Updated description of study-wise interim analyses.	Described the updated and streamlined statistical analyses

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
		schedule due to new enrollment timelines for part 2.
Appendix 2: Study Governance Considerations	Updated language surrounding clinical study report signatory. Added sections BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy and Data Security.	Correction of language. Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation requirement.
Entire Document	Editorial and formatting updates as needed.	For clarity.

Overall Rationale for Protocol Amendment 06, 01-Oct-2021

The key rationales of this protocol amendment are to: 1) optimize the statistical testing strategy for primary endpoints; 2) decrease the burden to the study participants and sites by reducing the frequency of tumor assessments after the first 2 years from randomization.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added title 'clinical trial physician' and 'clinical scientist' to document.	To align with new BMS naming convention.
Section 1-Summary	Summary to include all changes below where applicable. Also incorporated updates to the statistical language that were not incorporated in the previous amendment.	To align summary with changes below and to incorporate changes from protocol amendment 05 that were inadvertently missed.
Section 2- Schedule of Activities	Added language surrounding DPD testing under laboratory tests in Table 2-1.	To provide clarifying language
Section 2- Schedule of Activities	Reduced frequency of tumor assessments after first 2 years from randomization in Tables 2-2, 2-3, 2-4, 2-5, and 2-6 and added footnote.	Update made to reduce burden on study sites and study participants.
Section 2- Schedule of Activities	Updated every 6 months to every 6 cycles for SARs-CoV-2 testing in Tables 2-2, 2-3, 2-4, and 2-6.	Updated to align with study therapy administration schedule
Section 2- Schedule of Activities	Added language to allow endocrine function testing to be completed at preceding dosing visit to Tables 2-2 and 2-3. Added language to allow CEA and CA19-9 sample collection to be obtained at corresponding dosing visit or preceding dosing visit to Tables 2-2, 2-3, 2-4, and 2-6 and updated corresponding footnote.	Added to provide flexibility to study sites and study participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4 Objectives and Endpoints	Added new Table 4-1 for main estimands for primary and key secondary endpoints.	Added to address BMS internal decision on statistical analysis plan (SAP).
Section 5.1 - Overall Design	Added new paragraph about China sub-study.	Added to provide a reference in the Global protocol to China-sub-study described in China specific protocol amendment
Section 6.1-Inclusion Criteria and Section 6.3-Optional Crossover for Participants treated in the Arm C	Modified inclusion criteria to delete the following text “30 days [duration of ovulatory cycle] plus”	Correction to clarify the 5 month duration following last dose of study treatment is based on 5 half-lives of nivolumab.
Section 7-Treatment	Added additional ipilimumab dose 50 mg (5 mg/mL) in Table 7-1.	Added to align with upcoming drug product presentation.
Section 7.7.1- Prohibited and/or Restricted Treatments	Added language surrounding COVID-19 non-live vaccine benefit risk.	To align with program related changes.
Section 9.4-Safety and Section 9.4.4-Clinical Safety Laboratory Assessments	Updated language surrounding DPD-deficiency screening. Added DPD and SARS-CoV-2 to clinical safety and laboratory assessments table, and added wording ‘screening only’ after blood uracil.	To provide clarifying language.
Section 9.8-Biomarkers	Updated biomarker sampling schedule in Tables 9.8-1, 9.8-2, 9.8-3 from C4D15 to C4D1 and removed footnote.	To align collection dates with dosing visits.
Section 10.1-Sample Size Determination	Added word ‘initially’ before split.	To align with new updated statistical testing strategy per BMS internal comments on SAP.
Section 10.1.1-Sample Size Determination of Primary Endpoints	Changed 85% to 80% of the total number of PFS events. Added sub-headers and clarification languages for section “PFS in all lines for comparison between arms B vs A” and moved Table 10.1.1-2 after the first paragraph under “updated assumption”.	Typo correction To differentiate between initial assumptions and updated assumptions for clarification purpose.
Section 10.1.2-Power Calculation of Secondary Endpoints	Updated statistical language surrounding PFS and ORR.	To provide further clarification on the testing procedure on the key secondary endpoints.
Section 10.2-Populations for Analyses	Added statement on China extension sub-study analysis.	To clarify that participants enrolled in China sub-study after completion of global enrollment will not be included in the

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
		population for global CSR analyses.
Section 10.3- Statistical Analyses	Inserted new sub-heading 10.3.1-General Considerations' and added statement that primary and key secondary estimands are described in Table 4-1. Added statement surrounding analysis related to the China sub-study.	Added to address BMS internal comments on SAP. To clarify that the newly added China extension for China sub-study will not be included in the global CSR analyses.
Section 10.3.10-Strong control of Type I Error	Updated statistical language describing strong control of type I error. Updated figure 10.3.10-1 Testing procedure for primary and secondary endpoints.	To align with new updated statistical testing strategy per BMS internal comments on SAP.
Appendix 8-MSI Status Testing	Added list of next generation sequencing tests	To provide a list of NGS tests that can be used to determine MSI status locally.
Appendix 9-Country Specific Appendix	Updated language surrounding DPD-deficiency screening.	To provide clarity.
Appendix 2-Study Governance Considerations	Updated language on monitoring, dissemination of clinical data, clinical study report, and scientific publications.	Added to align with BMS standard protocol text and to provide clarity.
Appendix 13-Definition of pathological response.	Added new appendix section 13-Definition of pathological response.	To provide guidance to the sites for consistent reporting of pathological assessment of tumor regression in study participants undergoing curative intent surgery.
Entire Document	Editorial or formatting changes where appropriate.	To provide clarity.

Overall Rationale For Protocol Amendment 05, 18-Nov-2020

The protocol was updated to include dose modification criteria for immuno-oncology (I-O) therapy and I-O-related AE management algorithms based on version 5 of Common Terminology Criteria (CTCAE v5). Program-level updates were incorporated, including new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) study requirements, and male contraception requirements in connection with I-O therapy. Additional safety requirements for oxaliplatin were included.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added new Study Director.	New member joined 8HW study

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1- Synopsis	Updated instances referring to protocol v04 in the present tense. Updated to align with changes in the protocol body.	New protocol is v05.
Section 2- Schedule of Activities	Added SARS-CoV-2 AE assessments and serology testing within Section 2 tables.	Serum and AE/SAE collection in the context of SARS-CoV-2 was added to explore the impact of coronavirus disease 2019 (COVID-19) on study events/results.
Section 3.2.5- Nivolumab Mechanism of Action, Section 3.2.6- Ipilimumab Mechanism of Action	Added additional sentences describing nivolumab production and origin. Added additional text to paragraph.	Added to align with program-level updates.
Section 6.1- Inclusion Criteria	Edited language in inclusion criteria 1)a), 2)g), 3)e) and subsequent paragraph below.	Added to align with program-level updates and to provide clarity.
Section 6.2- Exclusion Criteria	Added clarifying language to exclusion criteria 2)i) and 3)e). Added exempt language under inclusion criteria (crossover cohort only) 2)e).	Aligned with updates to other parts of the protocol related to SARS-CoV-2 and program-level updates.
Section 7.1.2.4 -Crossover Cohort Nivolumab Plus Ipilimumab	Added text on observation time.	Added to provide clarity.
Section 7.4-Dosage Modification	Added Table 7.4-1 for AE criteria for delaying, resuming, and discontinuation of study treatment. Removed paragraph on guidance for dose modification for nivolumab and/or ipilimumab.	Reorganized dose delay, resume, and discontinuation criteria for improved readability and to align with CTCAE v5.
Section 7.4.1.1-Dose Delay Criteria for Nivolumab and/or Ipilimumab	Added suspected or confirmed SARS-CoV-2 infection as a criterion to delay treatment. Added paragraph on dose delay timing. Removed bullets relating to AE-related dose discontinuation criteria.	Updated dose delay criteria in cases of confirmed or suspected SARS-CoV-2 infection and to provide clarity.
Section 7.4.3.1- Criteria To Resume Treatment In Arm A, Arm B or Crossover Cohort	Modified text to align criteria for dose delay, resume, and discontinuation with Table 7.4-1, and added SARS-CoV-2 language. Removed bullets relating to AE-related dose. discontinuation criteria. Added language on ipilimumab treatment resumption.	Updated to align with CTCAE v5 and SARS-CoV-2 language and program-level updates.
Section 7.4.4- Management Algorithms for Nivolumab and Ipilimumab	Inserted new section with language to align with CTCAE v5 requirements.	Updated to align with CTCAE v5.
Section 7.4.6-Treatment of Treatment-related Infusion Reactions	Added statement on nivolumab and ipilimumab infusion reactions.	Added to provide clarity.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.1- Nivolumab and/or Ipilimumab Dose Discontinuation (Arm A, B or Crossover Cohort)	Added cross-reference to Table 7.4-1 and removed AE related dose discontinuation.	Updated to align with CTCAE v5.
Section 8.1.3-Treatment Beyond Progression for Participants in The Arms A, B or Crossover Cohort	Added statement on progression.	Added to align with program-level updates.
Section 9- Study Assessments and Procedures	Added paragraph on SARS-CoV-2 infection as well as additional language on cardiac and pulmonary toxicity.	Updated to align with SARS-CoV-2 recommendations and program-level updates.
Section 9.1.1-Imaging Assessments for the Study	Added statement on imaging for RECIST.	Added to align with program-level updates.
Section 9.2-Adverse Events	Added statement on AE and SAE reporting.	Updated to align with CTCAE v5.
Section 9.2.1-Time Period and Frequency for Collecting AE and SAE Information.	Added language surrounding AEs related to SARS-CoV-2 infection.	Updated to align with SARS-CoV-2 recommendations.
Section 9.2.3- Follow-up of AEs and SAEs	Added language surrounding AEs related to SARS-CoV-2 infection.	Updated to align with SARS-CoV-2 recommendations.
Section 9.4-Safety	Added statement on patient monitoring prior to oxaliplatin.	Added as an additional safety measure.
Section 9.5-Pharmacokinetics and Immunogenicity Assessments	Added additional paragraphs on blood sample collections.	Added to align with program-level updates.
Section 9.8.- Biomarkers	Added SARS-CoV-2 and additional timepoints for ctDNA collection.to biomarker sampling Tables 9.8-1, 9.8-2 and 9.8-3.	Updated to align with SARS-CoV-2 recommendations and to align with program-level updates.
Section 9.8.3- Soluble Markers	Added information related to SARS-CoV-2 serology testing.	Updated to align with SARS-CoV-2 recommendations.
Section 9.8.5- Additional Research Collection	Added additional paragraphs on additional research collection.	Added to align with program-level updates.
Appendix 4	Updated language related to contraception.	Added to align with program-level updates and corporate guidance.
Appendix 5	Updated I-O management algorithms.	Updated to align with CTCAE v5.
Entire document	Additional editorial or formatting changes, where appropriate.	Added to provide clarity.

Overall Rationale for Revised Protocol 04, 17-Jul-2020

This protocol revision is to expand enrollment of participants who have not received prior therapy. This extension will occur after completion of enrollment across lines of therapy. Thus study enrollment consists of 2 parts (enrollment across lines of therapy, part 1 enrollment, and extension of enrollment for participants who have not received prior therapy, part 2 enrollment). The protocol has been modified to incorporate the changes described below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1 -Synopsis	The synopsis has been modified to incorporate the changes described below	Updated to align with revised study design
Section 2-Schedule of Activities	Modified the laboratory test parameter row in Table 2-1. Added '(± 7 days)' under CEA and CA-19-9 assessment.	To clarify the timing of the respective tests
Section 2-Schedule of Activities	Added dose delayed statement to HEOR assessment rows in Tables 2-3 and 2-6	Added statement for consistency across study arms and periods
Section 2-Schedule of Activities	Added language on additional endocrine testing if clinically indicated, changed wording of Thyroid function test to Endocrine function test and added testing information throughout document and removed IRT drug vial assignments on C1D1 and C3D1 to Tables 2-2, 2-3, 2-4, and 2-6.	Change required per Japan specific label recommendation
Section 2-Schedule of Activities	Removed in IRT drug vial assessment on C1D22 and C2D1, C2D22 under cycles 1 and 2 in Table 2-3 and added review of concomitant medications, AE assessment, and laboratory tests in Table 2-4 upon PD.	Added to provide clarity.
Sections 3.1-Study Rationale, 3.1.1-Research Hypothesis, 3.2.3-Chemotherapy and targeted agents, 3.2.4-Nivolumab and Ipilimumab in dMMR/MSI-H Metastatic Colorectal Cancer: Check Mate 142 Study	Updated study rationale, hypothesis, background information with additional language and information.	Updated to align with revised study design
Section 4-Objectives and Endpoints	Updated primary and secondary study objectives and endpoints. In addition the CDx, crossover cohort and exploratory analysis were updated with new endpoints to evaluate efficacy, safety and PK.	Updated to align with revised study design.
Section 5.1 Overall Design	Updated overall study design with additional language and information on the part 1 and 2 enrollment. Study design schematic was updated and added a study conduct scheme.	Updated to reflect changes of revised study design

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2-Number of Participants	Updated number of participants	Updated for alignment with revised study design
Sections 5.4-Scientific Rationale for Study Design, 5.4.2-Rationale for Investigator's Choice Treatment and PFS assumptions in Chemotherapy Arm, 5.4.4-Rationale for Nivolumab and Ipilimumab Combination, 5.4.6-Rationale for Choice of Primary Endpoints	Study design updated to expand enrollment for participant who have not received prior therapy. Added additional scientific rationale to the study design and additional data under rationale	Updated for alignment with revised study design
Section 5.4.7-Clinical Validation of Companion Diagnostics	Added new section (5.4.7) on clinical validation of companion diagnostics	Added to provide additional rationale and background for companion diagnostics component of the study
Section 5.4.9-Rationale for Duration of Study Treatment	Added statement to clarify study duration for arm C participants	Added to provide additional clarity and rationale for study treatment duration in arm C
Sections 6.1-Inclusion Criteria, 6.2-Exclusion Criteria, 6.3-Optional crossover for participants treated in arm C	Inserted statement regarding inclusion criteria 2a, 2g and exclusion criteria 1b applicability to the study design. Added new exclusion criteria 2o on 'participants with DPD deficiency'. Removed <140/90mm Hg stated in exclusion criteria 2i. Added clarification statement to exclusion criteria 1b. Updated 6.2 and 6.3 -exclusion criteria 2e criteria to 2 yrs instead of 3 yrs	Added for alignment with revised study design (2a, 2g) and removed (1b) to reflect clinical practice. Added requirement for systematic DPD deficiency screening per French Authority for Health.
Section 7.1.1-Study Treatment Duration	Added statement (not applicable for arm C participants) to study treatment duration.	To clarify the treatment duration for arm C participants
Sections 7.1.2-Treatment Schedules, 7.1.2.2-Arm B Nivolumab Plus Ipilimumab (Q3Wx4), 7.1.2.3-Arm C Investigator's Choice Chemotherapy, 7.1.2.4-Crossover Cohort Nivolumab Plus Ipilimumab (Q6W continuously)	Added statement to include observation for approximately 30 minutes. Added statement that infusion start and stop times will be recorded in the CRF. Corrected cross reference from Table 7.1.2-1 to Table 7.1.2-4.	Updated to clarify the duration of observation before ipilimumab infusion.
Section 7.2.1-Initial Treatment Assignment	Added statement to clarify the randomization during part 1 and part 2 enrollment	Added for alignment with revised study design
Section 7.3-Blinding	Added statement surrounding generating aggregate reports	Added for clarity

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4-Dose Modification	Added new paragraph to clarify that dose modification criteria for nivolumab with or without ipilimumab should follow the CTCAE version 4, but reporting of the events intensity should follow CTCAE version 5. Added new paragraph on blood uracil and guidance for dose modifications	Added clarification regarding dose modifications/AE reporting and CTCAE versions. Added requirement for systematic DPD deficiency screening if locally mandated
Section 7.7.3-Surgical Resection Following Initial Response	Added paragraph with additional language around surgical resection.	Added for clarity.
Section 8.1.2-Investigator's Choice Chemotherapy Dose Discontinuation	Added new paragraph on dose delays lasting >6 weeks from previous dose	Added for clarity
Section 8.1.3-Treatment Beyond Progression for Participants in the Arms A, B or Crossover Cohort	Added statement to include 'Approval from BMS medical monitor or designee	Added as additional safety measure
Section 9.4-Safety, Section 9.4.4-Clinical Safety and Laboratory Assessments	Added statement on systematic screening for DPD deficiency. Updated laboratory assessment table to include additional information on chemistry tests, endocrine function tests and added blood uracil to panel, and CEA/CA19-9 assessments.	Added additional safety measures per local requirements
Section 9.5	Added statement 'up to 2 years of treatment' to tables 9.5-1, 9.5-2, and 9.5-3	Added to provide clarity on duration of samples collection
Section 10-Statistical Considerations	Updated all relevant statistical section to include detailed changes on the primary and secondary endpoints, sample size determination and power calculations, population analyses, efficacy analyses, safety analyses, crossover cohort analyses, interim and other analyses for parts 1 and 2 of the study design. Updated testing procedure figure 10.3.9-1 for primary and secondary endpoints	Changed for alignment with revised study design
Entire document	Additional editorial or formatting changes, where appropriate	Added to provide clarity
Appendix 5	Added myocarditis treatment algorithm	Update made to align with the most current nivolumab safety information.
Appendix 9	Removed France and Spain from criteria for exclusion of HIV positive participants. Added Tables to include France, Czech, and Japan specific language applicable to the protocol.	Update made to meet country-specific requirements in Spain and France. Additional country specific language tables were added as locally mandated.

Overall Rationale for Revised Protocol 03, 28-Mar-2019

The study design was amended to include the standard of care arm (SOC) that would allow to compare the efficacy and safety of immunotherapy vs chemotherapy in 1L and 2L settings in a prospective randomized study.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 2, Schedule of Activities, Table 2-1 Screening Procedural Outline	Update window of tissue collection acceptability to 3 months prior to enrolment instead of randomization. Clarify baseline tumor imaging to 28 days prior to randomization Note regarding urinalysis testing added.	Due to poor predictability of the randomization date and associated risk of the tumor tissue not being valid the timing for tumor tissue has updated to 3 months prior to enrolment Since pts in SOC arm may receive bevacizumab, note added about exclusionary levels of proteinuria.
Section 2, Schedule of Activities, Table 2-2 (Arm A, Table 2-3 (Arm B),	Added EORTC-QLQ-CR29 to the PRO collections. Added collection window for stool samples	Due to study design update the additional PRO assessment added. Stool sample collection window was added to clarify the allowable timing for sample collection.
Section 2, Schedule of Activities, On-treatment Procedural Outline, Table 2-4 (Arm C, Table 2-6 (Crossover Cohort),	Tables for Investigator Choice Chemotherapy, and Crossover Cohort added.	Updated due to updates in study design.
Table 2-5: Follow-Up Assessments	Added CBC with differential chemistry, thyroid function, and urinalysis. Tumor assessment timing updated. Clarification added regarding follow up visits for Arm C and Crossover Cohort	Clarified the lab assessments at the follow up visits. Tumor assessment timing updated to correct the mistake in prior version of the protocol.
Section 3.1 Study Rationale; Section 5.4 Scientific Rationale for Study Design; Section 5.4.2 Rationale for Investigators Choice Treatment in Chemotherapy Arm	Updated to contain the details and rationale regarding the inclusion of a third treatment arm.	Updated due to updates in study design.
Section 3.2.3 Chemotherapy in dMMR/MSI-H Metastatic Colorectal Cancer	Background on chemotherapy in participants with dMMR/MSI-H added.	Updated due to updates in study design.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3 Benefit Risk Assessment	Additional details regarding benefit risk of chemotherapy treatment in this population has been added.	Updated due to updates in study design.
Section 4, Objectives and Endpoints	Secondary and Exploratory objectives updated to evaluate comparisons with Arm C, and the Crossover Cohort	Updated due to updates in study design.
Section 5.1, Overall Design, Figure 5.1-1 Study Design Schema	Updated to incorporate the details of Arm C in into the study design. Updated to include the details of the optional Crossover Cohort. Updated schematic included	Updated due to updates in study design.
Section 5.2, Number of Study Participants; Section 10.1 Sample Size Determination	Number of participants updated to reflect in the incorporation of Arm C.	Updated due to updates in study design.
Section 5.4.1. Rationale for Treatment Setting	Rationale regarding first and second-line treatment settings added.	Updated due to updates in study design.
Section 5.4.5 Rationale for Optional Crossover from Chemotherapy Arm	Justification for Crossover Cohort for participants in Arm C was added.	Crossover cohort will ensure participants in Arm C have access to immunotherapy treatment.
Section 5.5 Justification for Dose	Justification for combination dosing of nivolumab and ipilimumab added.	To provide a rationale for continuous dosing of ipilimumab every 6 weeks (Q6W) in participants in the Crossover cohort
Section 6.1 Inclusion Criteria, Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Additional criteria added for participants that have received 0-1 prior therapy in the metastatic setting. Contraceptive guidance added for participants randomized to Arm C.	Updated due to updates in study design.
Section 6.2, Exclusion Criteria	Additional exclusion criteria added for participants who have received 0-1 prior line of therapy(2, h to n)	Updated due to updates in study design.
Section 6.2.1 Optional Crossover for Participants Treated in Arm C	Added specific criteria for participants in Arm C who will participate in Crossover Cohort	Updated due to updates in study design.
Section 6.3 Lifestyle Restrictions	Reference to SOC labels added.	Updated due to updates in study design.
Section 7 Treatment, Table 7-1 Study Treatments, Section 7.1.1, Study Treatment Duration; Table 7.1.2-3 Timing for	Added in study treatments for investigators choice chemotherapy, treatment durations and details for Investigators Choice Chemotherapy, and the Crossover Cohort, and details for treatment assignment.	Updated due to updates in study design.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Investigators Choice Chemotherapy, Section 7.1.2-4 Crossover Cohort; Section 7.1.2.3 Arm C-Investigators Choice Chemotherapy; Section 7.1.2.4 Crossover Cohort-Nivolumab Plus Ipilimumab (Q6WContinuously); Section 7.2.1 Initial Treatment Assignment; Section 7.2.2 Crossover Cohort Treatment Assignment		
Section 7.4 Dosage Medications; Section 7.4.1.2, Dose Delay for Investigators Choice of Chemotherapy; Section 7.4.1.2 Dose Delay Criteria for Investigators Choice of Chemotherapy; Section 7.4.2 Dose Reductions; Section 7.4.2.2. Dose Reductions for Investigators Choice Chemotherapy; Section 7.4.3.1 Criteria to Resume Treatment in Arm A, Arm B, or Crossover Cohort, Section 7.4.3.2 Criteria to Resume Treatment in Arm C; Section 7.7.1 Prohibited and/or Restricted Treatments; Section 8.1.2 Investigators Choice Chemotherapy Dose Discontinuation (Arm C).	Additional details on dosage modifications, dose reductions, and criteria to resume treatment added for Arm C Investigators Choice Chemotherapy and the Crossover Cohort. Updated prohibited treatments list to include restrictions for treatments to be administered in Arm C.	Updated due to updates in study design.
Section 9.1.1.2 BICR-Assessment of Progression	Language included regarding re-baseline assessment of the scans by BICR prior to enrollment in the Crossover Cohort.	Updated due to updates in study design.
Section 9.2.7 Potential Drug Induced Liver Injury	Removal of separate criteria for participants with elevated ALT/AST or total bilirubin at baseline	There is no uniformly accepted DILI criteria for participants with elevated ALT/AST or total bilirubin at baseline. In this situation to minimize the potential safety risk same criteria for potential DILI are applied to all patients.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5 Pharmacokinetics and Immunogenicity Assessments	Table 9.5-2 note regarding timing of collection, and clarification of dose delay. Table 9.5-3 Sampling schedule added for Crossover Cohort.	Updated to clarify sampling in the event of dose delay. Added an additional table to reflect the updates to study design.
Section 9.8 Biomarkers	Table 9.8-1, Sampling for Investigators Choice Chemotherapy (Arm C) Table 9.8-2- Biomarker Sampling Schedule for nivolumab plus ipilimumab Combination (Arm B), cycle length clarified. Table 9.8-3 Biomarker Sampling Schedule-Crossover Cohort added. Table 9.8-1 and Table 9.8-2- Collection window added for stool sample collection.	Updated due to updates in study design. Stool sample collection window was added to clarify the allowable timing for sample collection.
Section 10.1.1 Sample Size Determination of PFS comparison in Arm B vs Arm A	Updated to reflect the incorporation of the additional participants for randomization (Arm C)	Updated due to updates in study design.
Section 10.1.2 Power Calculation of PFS Comparison in Arm B vs. Arm C	Added in power calculation for comparison of Arm B vs Arm C	Updated due to updates in study design.
Section 10.2 Population for Analyses	Added investigator Choice Chemotherapy as a treated population. Added description of the Crossover Cohort	Updated due to updates in study design.
Section 10.3.1	Added definition of the exploratory endpoint investigator-assessed time to treatment failure (TTF) and time to treatment discontinuation (TTD).	Updated to enable the conduct of comparison of clinical study results and real world data
Section 10.3.3 Analyses or Crossover Cohort Treated Participants	Description of analyses for the Crossover Cohort added.	Updated due to updates in study design.
Section 10.3.9 Interim Analyses	Updated to reflect interim analysis of ORR and final analyses to incorporate Arm C into the details.	Updated due to updates in study design.
Appendix 10 Definition of Line of Therapy in CA2098HW Study	Updated to clarify definitions of line of therapy in CA2098HW study	To ensure consistency across participating sites in definition of the line of therapy that is one of the randomization factors.
Appendix 12 Guidance to sites on Tumor Location and Sidedness	Guidance on tumor sideness added.	Provided to assist sites in the assignment of tumor sideness to participants.

Overall Rationale for Revised Protocol 02

The Original Protocol and Revised Protocol 01 describe a single-arm, nivolumab monotherapy trial, and were never initiated. The current protocol (Revised Protocol 02) updates the design to a randomized trial of nivolumab vs nivolumab in combination with ipilimumab.

Overall Rationale for the Revised Protocol 01, 16-May-2018

This amendment extends eligibility to the subgroup of patients who received 5-FU, oxaliplatin and irinotecan all in the first line as a triplet chemotherapy combination (FOLFOXIRI).

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	Brief Rationale
Document History	Added Summary of changes	Document change to inclusion criteria.
Synopsis, Key Inclusion Criterion d); and Section 6.1: Inclusion Criterion 2) e	Revised inclusion criteria to include patients who received first line as a triplet chemotherapy combination (FOLFOXIRI).	Extends eligibility to the subgroup of patients who received first line as a triplet chemotherapy combination (FOLFOXIRI).
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

APPENDIX 12 GUIDANCE TO SITES ON TUMOR LOCATION AND SIDEDNESS

Please adhere to the following guidance when assigning tumor sidedness in eCRF and IRT transactions for participants enrolled to CA209-8HW:

Right Sided

- Cecum
- Ascending Colon
- Hepatic Flexure
- Transverse Colon
- Unknown OR Both-Sided locations

Left Sided

- Splenic Flexure
- Descending Colon
- Sigmoid Colon
- Rectum or Rectosigmoid Junction

Please note that the location of the primary tumor (not a metastatic site) should be used to define the sidedness.

APPENDIX 13 DEFINITION OF PATHOLOGICAL RESPONSE

Please adhere to the following definitions of pathological response in patients undergoing curative surgery on study CA209-8HW:

- Pathologic Complete response (pCR): no residual viable tumor cells
- Pathologic Major response (pMR): < 10% of residual viable tumor cells (≥ 90% reduction of the tumor cells)
- Pathologic Partial response (pPR): < 50% but ≥ 10% of residual viable tumor cells (≥ 50% reduction of tumor cells)
- Pathologic Non-response: ≥ 50% residual viable tumor cells (< 50% reduction of tumor cells)