Official Title of Study:

A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse

CheckMate 914: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 914

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CLINICAL PROTOCOL CA209914

A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse

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Protocol Amendment 06

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 06	08-Dec-2022	The purpose of Protocol Amendment 06 is to address the timing of interim and final disease-free survival (DFS) analyses in Part B, which were initially planned to occur at least 8 months of each other. However, the earlier versions of the protocol did not capture the scenario to proceed directly to the final DFS analysis in Part B in the event that the interim analysis and final analysis are projected in a shorter time interval (approximately within 6 months). With this amendment, the scenario with DFS final analysis only is explicitly stated. Also, the redundant OS interim analysis scenario in Part B is now omitted.
Protocol Amendment 05	13-Feb-2022	The purpose of Protocol Amendment 05 is to address the timing of interim and final disease-free survival (DFS) analyses in Part A, which were initially planned to occur within 6 months of each other. However, the earlier versions of the protocol did not capture the scenario to proceed directly to the final DFS analysis in Part A in the event that Part B enrollment is ongoing when the required number of events needed for interim analysis of DFS in Part A is achieved. With this amendment, the scenario with DFS final analysis only is pre-specified.
Administrative Letter 10	19-Feb-2021	Corrected language in Section 9.2.5, Pregnancy to ensure proper alignment throughout all sections of the protocol.
Administrative Letter 09	04-Jan-2021	• Updated Study Personnel • Clarifications to Synopsis and to Section 5.1, Overall Design • Corrected typographical errors in Section 10.3.4, Interim Analyses and Hierarchical Testing
Revised Protocol 04	27-Oct-2020	The purpose of Revised Protocol 04 is to remove Interim Analysis 1 for disease-free survival (DFS), from both Part A and Part B, to delay Interim Analysis 2 for DFS in Part A, and for both Part A and Part B Overall Survival (OS) to be hierarchically analyzed at the same time as the interim or final analysis for DFS in the same group of subjects. This revision also incorporates several changes to provide additional information and/or clarification to sections indicated. Some updates include clarifications and updates to contraception requirements, the clarification of timing for follow up visits and patient-reported outcomes collection, the addition of SARS-CoV-2 serology collection with a corresponding exploratory objective and endpoint, the addition of Appendix 9 regarding TNM staging and Fuhrman grading correlations, the incorporation of additional biomarker sample collections to better align with tumor assessments, collection of tumor necrosis status which will allow for SSIGN score assessments, and an extension of the required length of time to collect adverse events (AEs) (serious adverse events [SAEs] or non-serious AEs) considered related to the study therapy. This revision also incorporates Administrative Letter 08.
Administrative Letter 08	05-Feb-2020	Advises sites of inadvertent omission to Revised Protocol 03 of changes made to protocol in Administrative Letters 05 and 07. Although changes were omitted, they were still effective.
Revised Protocol 03	01-Nov-2019	The purpose of Revised Protocol 3 is to add Part B to the study for evaluation of nivolumab monotherapy. Also incorporates Administrative Letter 06

Administrative Letter 07	05-Feb-2019	Update Appendix 4
Administrative Letter 06	16-Nov-2018	Study Personnel Updates
Administrative Letter 05	01-Aug-2018	Correct typographical errors in Sections 6.1 and 7.2, and corresponding sections of the synopsis.
Revised Protocol 02	**0**6-Apr-2018	The purpose of this revised protocol is to reduce frequency of patient questionnaires, update exclusion criterion for serum creatinine, remove 42-day screening window, provide more flexibility in scheduling scans, update background data, and provide additional information and/or clarification to sections indicated.
Administrative Letter 03	28-Mar-2018	The main purpose of this letter is to update the information related to a change in the Medical Monitor for this study.
Administrative Letter 02	16-Nov-2017	The main purpose of this letter is to update the information related to a change in the Medical Monitor for this study.
Administrative Letter 01	28-Jun-2017	The main purpose of this letter is to correct a typographical error in Exclusion Criteria 2b and 4a in Revised Protocol 01, dated 22-Mar-2017.
Revised Protocol 01	22-Mar-2017	Incorporates Amendment 01
Amendment 01	22-Mar-2017	• Consider the placebo products as investigational products • Remove the bioequivalence language
Original Protocol	14-Feb-2017	Not Applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 06:

The purpose of Protocol Amendment 06 is to address the timing of interim and final disease-free survival (DFS) analyses in Part B, which were initially planned to occur at least 8 months apart from each other. However, the earlier versions of the protocol did not capture the scenario where the interim and final analyses of DFS in Part B are projected to occur in a shorter time interval (approximately within 6 months).

Therefore, this amendment for Part B is being issued to allow the possibility of conducting only the final DFS analysis without the interim DFS analysis in the event these two analyses in Part B would occur within 6 months of each other. Table 10.1.2 provides details on the alpha, critical hazard ratio, and target number of events for this scenario. A 6-month period was determined as the threshold based on the operational considerations of this 3-arm study part. Overall, this amendment for Part B is similar to Protocol Amendment 05, which added a similar scenario for Part A.

Additionally, wording clarifications have been made for the interim overall survival (OS) analyses in Part B. If the first interim OS analysis were to reach the statistical significance with approximately 102 events, then the study would stop for early superiority for the formal OS comparison, and second interim OS analysis with approximately 127 events would not be performed. Due to this reason, the scenario with 127 OS events is redundant, and it is now omitted from the protocol to simplify the interim OS analyses plan in Part B. With this update, it is now clearly stated that the interim OS analyses in Part B are to be based on 102 and 146 events, as initially planned.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.1 Part A: Combination Comparison of DFS	Typographical error has been updated within the section to align with values presented in Table 10.1.1-1.	Typographical error has been corrected.
Section 10.1.2: Part B: Monotherapy Comparison of DFS Table 10.1.2-2: Part B Summary of Sample Size Parameters and Schedule of Monotherapy (without an Interim Analysis) Section 10.3.4: Interim Analyses and Hierarchical Testing	Parameters and schedule of analysis for final DFS analysis alone in Part B were added. Also, summary Table 10.1.2-2 was added.	In the event that the target number of events needed for the final analysis is projected in a shorter time interval (approximately within 6 months), the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted in Part B.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.4: Interim Analyses and Hierarchical Testing	Language of the Part B OS interim analyses is clarified and one of the scenarios for the second interim OS analysis in Part B is omitted.	The Part B OS interim analyses language is updated to clearly state the plan for the pre-specified interim analyses. Also, OS interim analysis with approximately 127 events is a redundant scenario, and it is now omitted.
Section 10.3.1: Efficacy Analyses	Stratum(s) with small number of participants.	In the event that there are fewer subjects randomized to a stratum, the participants in the stratum will be combined into another stratum.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse

Short Title: CheckMate 914: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 914

Study Phase: 3

Rationale:

The current standard treatment for early stage (I-III) renal cell cancer (RCC) is surgery. While the prognosis of stage I tumors is excellent, stage II and particularly stage III have a high risk of relapse and represent a high unmet medical need.

The clinical activity of nivolumab and nivolumab plus ipilimumab observed to date in advanced RCC include 1 positive Phase 3 study demonstrating prolonged survival with nivolumab monotherapy compared to everolimus in metastatic RCC and significant improvement in OS with nivolumab plus ipilimumab compared with sunitinib in the Checkmate 214 study. Based on the Checkmate 214 study results, the combination of nivolumab and ipilimumab is approved by the US Food and Drug Administration (FDA) for the treatment of intermediate- and poor-risk, previously untreated patients with advanced RCC, and it is incorporated into the European Association of Urology guidelines. These results suggests the potential for improved clinical outcomes also in the adjuvant setting. In 2015, nivolumab was approved in the United States for the treatment of metastatic RCC in patients who previously received anti-angiogenic therapy.

The study CA209914 aims to explore the role of the nivolumab and ipilimumab combination compared to placebo and the role of nivolumab monotherapy compared to placebo post-surgery in added efficacy and safety in preventing disease recurrence and the impact on survival.

If the safety profile is acceptable and nivolumab monotherapy or nivolumab combined with ipilimumab is shown to improve DFS, this study would support the approval of nivolumab or nivolumab combined with ipilimumab in treatment-naive advanced RCC patients post-surgery.

Study Population:

Participants with predominately clear cell RCC who have had a nephrectomy will be included.

Key Inclusion Criteria:

a) Kidney tumor has been completely resected with negative surgical margins obtained. The randomization must occur greater than 4 weeks and less than (or equal to) 12 weeks from the date of nephrectomy. Partial nephrectomy is allowed provided all inclusion criteria are met.
b) Post-nephrectomy tumor shows RCC with a predominately clear cell histology, including participants with sarcomatoid features.

c) Pathological TNM staging per AJCC staging version 2010 (refer to Appendix 9 for correlations of classifications in cancer staging systems):
   - pT2a, G3 or G4, N0M0
   - pT2b, G any, N0M0
   - pT3 (a, b, c), G any, N0M0
   - pT4, G any, N0M0
   - pT any, G any, N1M0

d) Participants must have no clinical or radiological evidence of macroscopic residual disease or distant metastases (M0) after nephrectomy
   i) Baseline tumor assessment, performed 4 to approximately 12 weeks after nephrectomy, shows no metastasis or residual tumor lesions per local review and as confirmed by Blinded Independent Central Review (BICR). Results of BICR of the baseline tumor assessment confirming absence of metastasis or residual tumor lesions must be received before randomization.

      Note: participants with one or more regional lymph nodes identified with short axis ≥ 15 mm on the baseline (post-operative) tumor assessments are considered to have gross residual disease and are therefore ineligible.

e) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 (Appendix 5).

f) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 3 months prior to enrollment, preferably from nephrectomy, with an associated pathology report, must be submitted to the central laboratory prior to randomization. FFPE block or 20 unstained slides is ideal, but a minimum of 10 unstained slides will be acceptable if tumor tissue is limited. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is unacceptable for submission.

Key Exclusion Criteria

a) Any severe or serious, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration including ongoing or active infection requiring parental antibiotics

b) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Topical, ocular, intra-articular, intranasal, inhaled steroids, and adrenal replacement steroid doses > 10 mg daily prednisone or the equivalent are permitted in the absence of active immune disease.

c) Uncontrolled adrenal insufficiency

d) 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.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• Part A: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC, with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab versus placebo infusions in participants with localized renal cell carcinoma, with a predominantly clear cell histology who have undergone nephrectomy.	The primary endpoint is DFS. The primary endpoint of DFS will be programmatically determined based on the disease recurrence date provided by the BICR. DFS is defined as the time from randomization to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary RCC primary cancer), distance metastasis, or death, whichever came first.
Secondary	
• Part A: To compare OS, including the 5-year OS rates, of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To compare overall survival (OS), including the 5-year OS rates, of nivolumab versus placebo infusions in participants with localized renal cell carcinoma with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To evaluate differences in disease-free survival (DFS) per Blinded Independent Central Review (BICR) and overall survival (OS) of contemporaneously randomized nivolumab combined with ipilimumab participants versus nivolumab participants with localized renal cell carcinoma, with a predominantly clear cell histology, who have undergone a nephrectomy.	• OS, defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the participants was known to be alive. • DFS and OS in contemporaneously randomized combination and monotherapy participants.
• To describe the safety and tolerability of nivolumab combined with ipilimumab and nivolumab monotherapy up to 30 and 100 days of last dose of study therapy.	• Safety and tolerability endpoint: type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0], timing, seriousness, and relatedness, and laboratory abnormalities up to 30 and 100 days of last dose of study therapy in all treated participants

Overall Design:

The original study design (Part A) is a double-blind, randomized trial of the nivolumab and ipilimumab combination therapy versus placebo infusions in participants with early stage localized RCC with a predominantly clear cell histology who underwent radical or partial nephrectomy. Approximately 1000 participants will be screened, and approximately 800 participants will be randomized.

At the implementation of Revised Protocol 03, Part A of the study remains identical to the original protocol design. The addition of Part B to the protocol includes a monotherapy nivolumab arm. A target of approximately 800 participants are planned to be randomized between 3 arms in a 1:1:2 ratio in Part B, with the primary endpoint of DFS and secondary endpoints of OS, and safety and tolerability.

Approximately 1600 participants in total are expected to be randomized in this study.

TNM staging will be stratified according to the following characteristics:

- pT2a, G3 or G4, N0, M0 and pT2b, G any, N0, M0
- pT3, G any, N0, M0
- pT4, G any, N0, M0 and pT any, G any, N1, M0

Randomization must occur greater than 4 weeks and less than (or equal to) 12 weeks from the date of nephrectomy.

Tumor tissue obtained within 3 months prior to enrollment, preferably at the time of the nephrectomy, must be provided for biomarker analyses.

Screening/baseline imaging should be performed at least 4 weeks post-nephrectomy- and submitted to the radiology vendor for BICR confirmation of disease-free status. Pre-nephrectomy images are also requested, if available. Participant eligibility must be confirmed by BICR prior to randomization and will be based only on the review of the baseline scans (and pre-nephrectomy scans if available). As a result, pre-nephrectomy scans, if available, and baseline scans are encouraged to be submitted to BICR within 8 weeks of the nephrectomy to allow for timely return of the decision from the BICR.

The Treatment Phase begins when the randomization call is made into the Interactive Response Technology (IRT).

For Part A of the study:

- Arm A: nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions

For Part B:

- Arm A: nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions
- Arm C: Nivolumab 240 mg every 2 weeks and ipilimumab placebo every 6 weeks (or every third nivolumab dose if dosing is delayed)

Treatment must be completed within 36 weeks after the first dose; any cycles not received within 36 weeks after the first dose will be omitted, and the participant will enter the Follow-up Phase.

Tumor assessments will occur in accordance with the Schedule of Activities or until recurrence has been identified by the investigator and is confirmed by BICR. Sites should submit all scans to the third-party vendor on a rolling basis, preferably within 7 business days of scan acquisition, and submit any pertinent cytology/pathology report for central review. PK and immunogenicity samples, biomarker assessments, and NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) and EuroQoL's EQ-5D-3L will be collected according to the Schedule of Activities. Adverse event (AE) assessments should be documented at each clinic visit.

The Follow-up Phase begins at the completion of 12 cycles, when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy), or at Week 36, whichever comes first. Participants will have 2 follow-up visits (Follow-up 1 and Follow-up 2) for safety within 30 (± 7 days) and 100 days (± 7 days), respectively, from the last dose of study therapy. If the date of discontinuation is greater than 30 days after last dose, the Follow-up visit 1 can coincide with the date of discontinuation (± 7 days). Any ongoing treatment related- AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible. After the Follow-up 2 Visit, all participants will be followed for overall survival status every 12 weeks (± 1 week) until death, withdrawal of consent, lost to follow-up, or end of study.

Figure 1: CA209914 Study Design Schematic for Part A

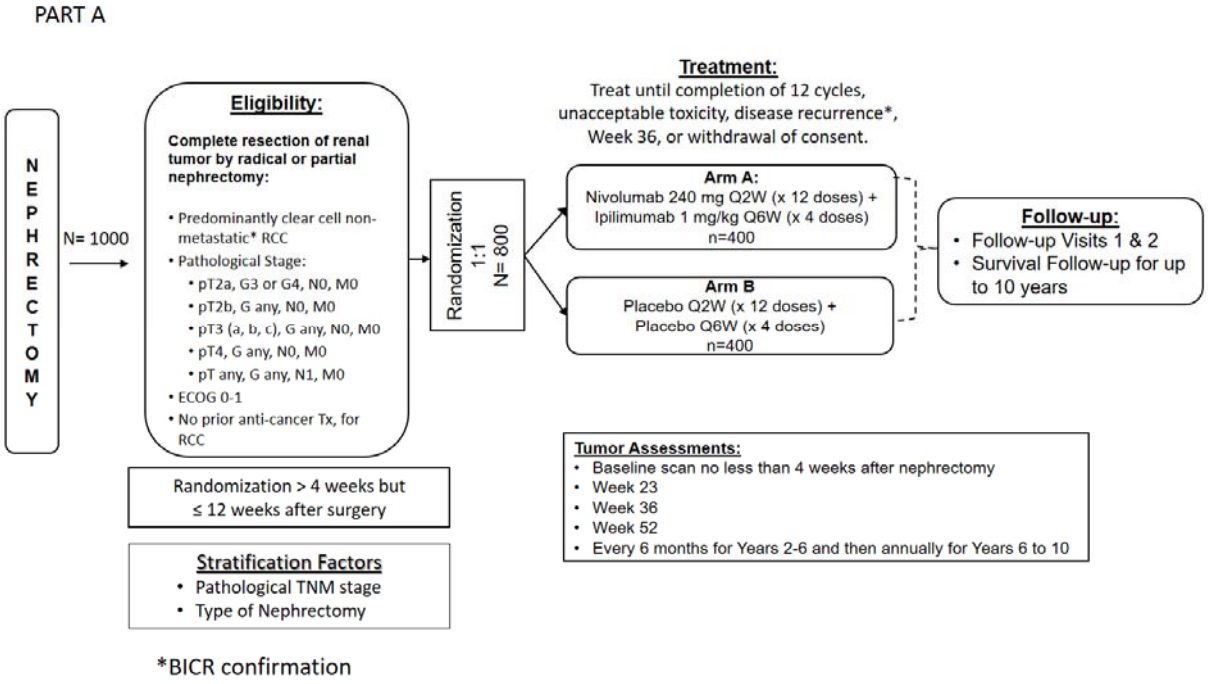
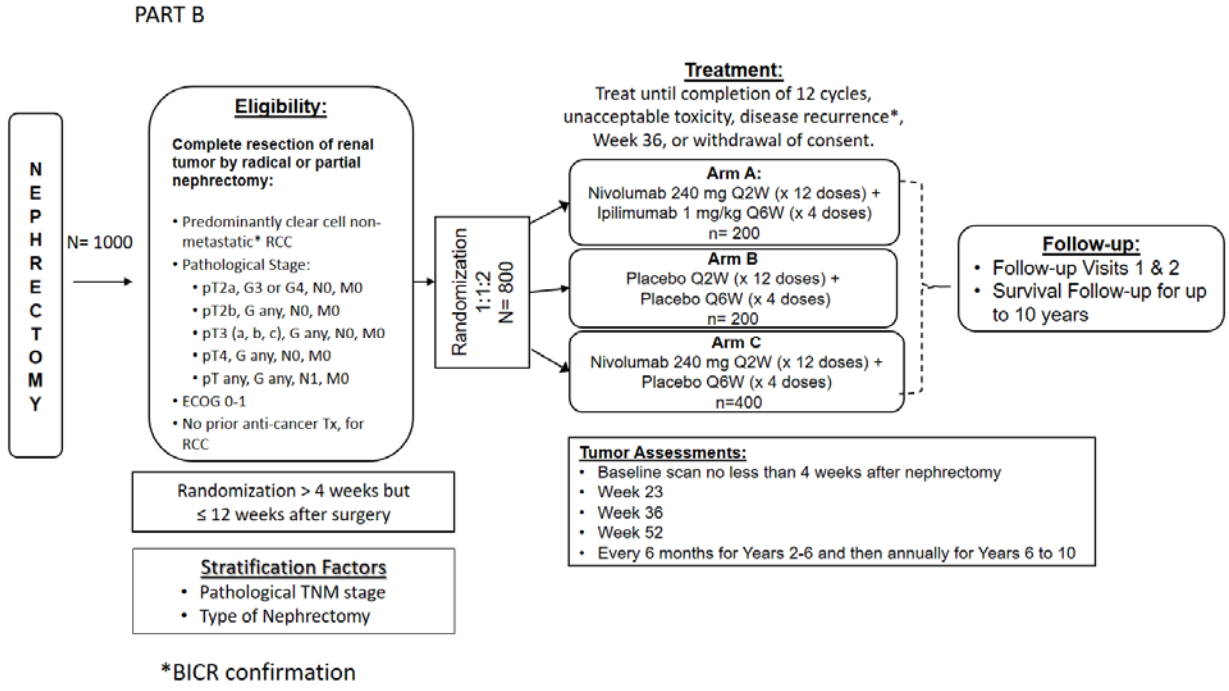


Figure 2: CA209914 Part B Study Design Schematic



Number of Participants:

Approximately 1600 participants will be randomized in this study, 800 participants in Part A and 800 participants in Part B.

Treatment Arms and Duration:

For Part A of the study:

- Arm A: Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions

For Part B of the study:

- Arm A: Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions
- Arm C: Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed)

Each cycle will be 2 weeks (14 days). Participants will receive study drug until the end of 12 cycles (12 nivolumab doses and 4 ipilimumab doses), recurrence, unacceptable toxicity, 36 weeks after

first dose, or withdrawal of consent, whichever occurs first. The first cycle will be a combination dose.

Study Treatment:

Study Drug for CA209914		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	IP
Ipilimumab	200 mg (5 mg/mL)	IP
0.9% Sodium Chloride for Injection	NA	IP
5% Dextrose for Injection	NA	IP

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209914. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

Blinded Independent Review Committee:

The BICR will review tumor images and pertinent clinical data (cytology/pathology report) in all randomized participants to determine eligibility and response for the DFS analyses. Details of the BICR responsibilities, procedures, composition, and process will be specified in the BICR charter.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA209914) All Participants

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain participant number.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study.
Safety Assessments		
Full Physical Examination, Measurements, Vital Signs, and Performance Status	X	Includes height, weight, ECOG Performance Status (Appendix 5), BP, HR, and temperature within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Review of Concomitant Medications	X	Within 14 days prior to randomization. Document vaccine use within 30 days prior to first dose of study treatment. See Section 6.2 and Section 7.7 for additional details.
Serious Adverse Events (SAE) Assessment	X (see Notes)	Collect Serious Adverse Events from time of consent. In addition, collect all AEs (SAEs and non-serious AEs) associated with suspected or confirmed SARS-CoV-2 infection from time of consent.
Laboratory Tests		
Laboratory Test	X	Must be performed within 14 days prior to randomization: • CBC w/differential • Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, phosphate, Ca, Na, Mg, K, Cl, LDH, glucose, and albumin • Thyroid panel including TSH, Free T4, Free T3 • Hep B/C (HBVsAg, HCV antibody or HCV RNA) • (sites in countries or locals where HIV testing is required, see Appendix 7)

Table 2-1: Screening Procedural Outline (CA209914) All Participants

Procedure	Screening Visit[a]	Notes
Pregnancy Test	X	WOCBP only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose of study therapy.
Efficacy Assessments		
Baseline Tumor Assessments	X	CT/MRI of the chest, abdomen, and pelvis. See Section **9.1.3.1**. Baseline assessments should be taken no less than 4 weeks after the nephrectomy, and sites are strongly encouraged to submit scans to the Blinded Independent Central Review (BICR) preferably within 8 weeks after the nephrectomy to allow for return of the results from the BICR. Pre-nephrectomy images are also requested, if available, and should be submitted to the BICR within 8 weeks post-nephrectomy. BICR confirmation of disease-free status is required prior to randomization.
Tumor Tissue Samples	X	Submission of sufficient tumor tissue, preferably obtained from the nephrectomy, with associated pathology report will be required. Formalin-fixed, paraffin-embedded (FFPE) block or 20 unstained slides, a minimum of 10 slides will be acceptable if tumor tissue is limited (see Section **9.8.2**).

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, Blinded Independent Central Review; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood count; Cl, chloride; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HBVsAg, hepatitis B surface antigen; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; IRT, Interactive Response Technology; LDH, lactate dehydrogenase; K, potassium; Mg, magnesium, NA, sodium; SAE, serious adverse event; T.Bili, total bilirubin; WOCBP, women of childbearing potential.

[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.

Table 2-2: On-treatment Procedural Outline (CA209914) Part A and Part B

Procedure	Cycle 1 Day 1 (Nivolumab + Ipilimumab)	Cycles 2, 3, 5, 6, 8, 9, 11, & 12 Day 1[a,b] Each Cycle = 2 weeks (Nivolumab alone)	Cycles 4, 7, & 10 Day 1, (Nivolumab + Ipilimumab)	Notes
Safety Assessments				
Targeted Physical Examination, Vital Signs, and Performance Status	X	X	X	Weight, BP, HR, temperature, and ECOG Performance Status (Appendix 5) to be performed within 72 hours prior to dosing
Assessment of Signs and Symptoms	X	X	X	
Adverse Event (AE)Assessment and Serious Adverse Event (SAE) Assessment	Continuously (see Notes)			Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events (SAEs and non-serious AEs), including those associated with suspected or confirmed SARS-CoV-2 infection, will be collected continuously during the treatment period and documented for a minimum of 100 days after last dose (Appendix 3).
Review of Concomitant Medications	X	X	X	Record at each visit.
Laboratory Tests	X	X	X	Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to first dose. After C1D1, within 72 hours prior to dosing and results should be reviewed prior to administration of each dose of study drug: • CBC w/differential. • Chemistry panel including AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, phosphate, Ca, Mg, Na, K, Cl, LDH, glucose, and albumin. • TSH (with reflexive Free T4 and Free T3).

Table 2-2: On-treatment Procedural Outline (CA209914) Part A and Part B

Procedure	Cycle 1 Day 1 (Nivolumab + Ipilimumab)	Cycles 2, 3, 5, 6, 8, 9, 11, & 12 Day 1[a,b] Each Cycle = 2 weeks (Nivolumab alone)	Cycles 4, 7, & 10 Day 1, (Nivolumab + Ipilimumab)	Notes
Pregnancy Test	X	X	X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks, regardless of dose delay. Serum or Urine. WOCBP only.
Pharmacokinetic Samples				
PK Samples	X	X		See **Table 9.5-1**. At Cycles 1, 2, 5, 8, & 11.
Immunogenicity blood sample	X	X		See **Table 9.5-1**. At Cycles 1, 2, 5, 8, & 11.
Exploratory Biomarker Assessments				
Whole Blood (DNA)	X			Only at baseline.
Serum	X		X	Prior to dosing. At Cycle 1, 4, and 7, and upon occurrence of ≥ Grade 3 non-laboratory drug-related AE and/or lab abnormalities regarded as a drug-related SAE, to be collected when clinically safe and feasible.
ctDNA	X	X (C2D1, C5D1, C9D1 only)		Samples should be collected prior to dosing. Subsequent sample collections will be aligned with tumor assessments performed on Weeks 23, 36, and 52 (± 1 week window). If a tumor assessment is not performed, ctDNA sampling is not required.
Peripheral Blood RNA	X			Prior to dosing at Cycle 1 and upon ≥ Grade 3 non-laboratory drug-related AE and/or laboratory abnormalities regarded as a drug-related SAE, to be collected when clinically safe and feasible.
Myeloid Derived Suppressor Cells	X		X	Cytochex Tube. Prior to dosing. At Cycle 1 and 7.

Table 2-2: On-treatment Procedural Outline (CA209914) Part A and Part B

Procedure	Cycle 1 Day 1 (Nivolumab + Ipilimumab)	Cycles 2, 3, 5, 6, 8, 9, 11, & 12 Day 1[a,b] Each Cycle = 2 weeks (Nivolumab alone)	Cycles 4, 7, & 10 Day 1, (Nivolumab + Ipilimumab)	Notes
SARS-CoV-2 Serology	X	X (C12D1 only)		Samples should be collected prior to dosing. Serum will be collected at C1D1 and C12D1 for all participants, and approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or immunoglobulin G (IgG) [see Section 9.8.9]). If a suspected or confirmed SARS-CoV-2 infection occurs within 4 weeks of the C1D1 or C12D1 time point, a single serum sample will be collected to satisfy the requirements for both the C1D1 or C12D1 and approximately 4 week after infection time points.
Efficacy Assessments				
Tumor Assessments	See Notes.			CT/MRI of the chest, abdomen, and pelvis. Assessment should be performed at Weeks 23, 36, and 52 (± 1 week) regardless of any dose delays. Use same imaging method as was used at screening/baseline. See Section **9.1.3** for additional details.
Patient-Reported Outcomes				
EQ-5D-3L	X	Cycles 3, 6, 9, and 12		Completed on Day 1 of Cycles 1, 3, 6, 9, and 12 prior to any study-related procedures.
FKSI-19	X[c]	Cycles 3, 6, 9 and 12		Completed on Day 1 of Cycles 1, 3, 6, 9, and 12 prior to any study-related procedures.

Table 2-2: On-treatment Procedural Outline (CA209914) Part A and Part B

Procedure	Cycle 1 Day 1 (Nivolumab + Ipilimumab)	Cycles 2, 3, 5, 6, 8, 9, 11, & 12 Day 1[a,b] Each Cycle = 2 weeks (Nivolumab alone)	Cycles 4, 7, & 10 Day 1, (Nivolumab + Ipilimumab)	Notes
Drug Administration				
Randomize	X			Begins with call to Interactive Response Technology.
Administer nivolumab or placebo	X	X	X	Participants must begin study treatment within 3 calendar days of randomization.
Administer ipilimumab or placebo	X		X	Participants must begin study treatment within 3 calendar days of randomization.

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; C1D1, Cycle 1 Day 1; Ca, calcium; CBC, complete blood count; Cl, chloride; ECOG, Eastern Cooperative Oncology Group; FKSI-19, Functional Assessment of Cancer Therapy - Kidney Symptom Index; HR, heart rate; LDH, lactate dehydrogenase; K, potassium; Mg, magnesium, NA, sodium; SAE, serious adverse event; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; T.Bili, total bilirubin; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[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] If all cycles are not given within 36 weeks after the first dose, the participant will discontinue treatment and move to Post-treatment Follow-up.

[c] Note: at baseline visit (C1D1) only, Question GP5 on FKSI-19 can be left blank as participant has not yet received treatment.

Table 2-3: Post-treatment Follow-up (CA209914) Part A and Part B

Procedure	Follow-Up Visit 1 and 2[a]	Survival Follow-Up[b]	Notes
Safety Assessments			
Targeted Physical Examination, Vital Signs, and Performance Status	X		Weight, BP, HR, temperature, and ECOG Performance Status (Appendix 5).
Assessment of Signs and Symptoms	X		
Adverse Event (AE) Assessment and Serious Adverse Event (SAE) Assessment	X	See Notes	Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All AEs will be documented for a minimum of 100 days after last dose (Appendix 3). 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 suspected or confirmed SARS-CoV-2 infection and study treatment-related AEs (SAEs and non-serious AEs) until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases of SARS-CoV-2, until SARS-CoV-2 infection is ruled out. Also, all non-serious AEs considered related to the study treatment should be collected through survival follow-up visits until approximately 1 year following discontinuation of study treatment (see Section 9.2.1 and Section 9.2.3 for additional details).
Review of Concomitant Medications	X	X	During survival follow-up any new anti-tumor therapy initiated for either disease recurrence or a secondary malignancy at any time during this period will be captured in the CRF

Table 2-3: Post-treatment Follow-up (CA209914) Part A and Part B

Procedure	Follow-Up Visit 1 and 2[a]	Survival Follow-Up[b]	Notes
Laboratory Tests	X		CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, phosphate, Ca, Mg, Na, K, Cl, LDH, glucose, and TSH (with reflexive Free T4 and Free T3).
Pregnancy Test	X		Serum or Urine. WOCBP only.
Pharmacokinetic Samples			
PK Samples	X		
Immunogenicity blood sample	X		
Exploratory Biomarker Assessments			
Serum	See Notes		Upon disease recurrence or occurrence of ≥ Grade 3 non-laboratory drug-related AE and/or lab abnormalities regarded as a drug-related SAE, to be collected when clinically safe and feasible
Peripheral Blood RNA	See Notes		Upon disease recurrence or occurrence of ≥ Grade 3 non-laboratory drug-related AE and/or lab abnormalities regarded as a drug-related SAE, to be collected when clinically safe and feasible.
ctDNA	See Notes		Sample collection is aligned with the tumor assessments on Weeks 23, 36, and 52 (± 1 week window). If a tumor assessment is not performed, ctDNA sampling is not required.
SARS-CoV-2 Serology	See Notes		Serum will be collected at Follow-up visit 2 only for all participants, and approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8.9]). If a suspected or confirmed SARS-CoV-2 infection occurs within 4 weeks of the follow-up visit 2 time point, a single serum sample will be collected to satisfy the requirements for both the follow-up visit 2 and approximately 4 week after infection time points.

Table 2-3: Post-treatment Follow-up (CA209914) Part A and Part B

Procedure	Follow-Up Visit 1 and 2[a]	Survival Follow-Up[b]	Notes
Tumor Biopsy	See Notes		Tumor biopsy collection at the time of recurrence is optional but highly encouraged.
Efficacy Assessments			
Tumor Assessments	See Notes		• Timing for scans should be based on date of first treatment, which is considered Week 1. Weeks 23, 36, and 52 (± 1 week window at each time point). • After Week 52 (first year), tumor assessments should occur every 6 months (± 2 week window) until Year 6. • Annually for Year 6 to Year 10 (± 2 week window). • Additional imaging of potential disease sites should be performed whenever disease recurrence or occurrence of a secondary malignancy is suspected. • Tumor assessments can be discontinued when recurrence has been confirmed by BICR. • Brain CT or MRI with contrast or bone imaging (confirmatory imaging in addition to bone imaging may be required) if clinically indicated. • See Section 9.1.3 for additional details.
Patient-Reported Outcomes			
EQ-5D-3L	X[c] (see Notes)	See Notes[c]	Perform at Follow-up 1 and 2, the first Survival Visit and at every other survival Follow-Up visit thereafter (Survival Follow-up visit 3, 5, 7, etc).[c] All patient-reported outcomes should be completed prior to study-related procedures, if possible.
FKSI-19	X[c] (see Notes)	See Notes[c]	

AE, Adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood count; Cl, chloride; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FKSI-19, Functional Assessment of Cancer Therapy - Kidney Symptom Index; HR, heart rate; LDH, lactate dehydrogenase; K, potassium; Mg, magnesium, NA, sodium; SAE, serious

adverse event; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; T.Bili, total bilirubin; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit 1 (Follow-up 1) = 30 days from the last dose ± 7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up visit 2 (Follow-up 2) = 100 days (± 7 days) from the last dose of study medication.

[b] From Follow-up 2, all participants will be followed for overall survival status every 12 weeks (± 7 days) until the time for the final analysis. Survival status can be ascertained by telephone contact if the participant is unable to return to the site. If new anti-tumor therapy is initiated for either disease recurrence or a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate Case Report Form (CRF).

[c] If participant is unable to perform the patient-reported outcome assessment in person, the EQ-5D-3L and FKSI-19 can be performed via telephone. The same window (± 7 days) applies for telephone contacts.

3 INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common cancer in the world with an increasing incidence.[1] In the United States, there were approximately 63,000 new cases in 2015 and almost 14,000 deaths.[2] There were approximately 84,000 cases of RCC and 35,000 deaths due to kidney cancer in 2012 in the European Union.[3,4] Despite the earlier detection of smaller kidney tumors, the rate of RCC-related mortality has increased,[5,6] suggesting that recurrence and advanced disease are responsible for mortality. In this context, optimizing the management of early-stage RCC, as well as advanced RCC, are key priorities in the oncological clinical practice.

When RCC is localized early in the course of the disease, it is well established that radical surgical resection is curative for a proportion of patients however, it is estimated that 20-30% of patients will experience relapse.[16] Most relapses occur within 3 years after surgery, with a median time of 1-2 years however; recurrences have been reported through 30 years.[16] Prognostic factors that have been associated with an increased risk of recurrence include anatomic extent of disease, histopathology, presence of tumor necrosis, and certain biomarkers.[7] Effective adjuvant therapy, in addition to surgical management, may offer an alternative approach to the standard of care for patients with high risk of recurrence. Investigational research is currently ongoing regarding prognostic factors, time and risk of recurrence, and use of adjuvant therapy in the localized RCC setting.

Several trials have shown no benefit with adjuvant interferon- or interleukin-2-based therapies or a CA-IX antibody. This is in contrast to a number of clinically proven therapies for stage IV RCC.

Additional trials are currently assessing the efficacy of the approved multi-targeted tyrosine kinase inhibitors, including sorafenib (SORCE) and axitinib (ATLAS) (Table 3-1), in the adjuvant setting.

Table 3-1: Clinical Trials Database Listed Large, Multicenter, Placebo-Controlled, Randomized, Double-blind, Adjuvant Clinical Trials in RCC (Completed)

Acronym	Trial No.	Status	Intervention	Funding Body/ Sponsors	Design	Start Date/ Est Complete Date	Stratification	Estimated Enrollment	Outcome Measures
ARISER	NCT00087022	Completed	Girentuximab	Industry; Wilex	MC, DB, R, PC	07/2004 10/2012	High-risk patients based on TN stage or Fuhrman grade, ECOG PS = 0 or 1	864	Primary endpoint DFS, not met
ASSURE	NCT0326898	Completed	Sorafenib or Sunitinib	NIH; NCI, ECOG, SWOG, Cancer and Leukemia Group B, NCIC	MC, DB, R, PC	05/2006 04/2016	At least intermediate high-risk UISS, ECOG PS = 0 or 1, clear or non-clear cell RCC	1923	Primary endpoint DFS not met
ATLAS	NCT01599754	Terminated	Axitinib	Industry; SF J Pharma., Pfizer	MC, DB, R, PC	04/2012 05/2019	High-risk UISS, ECOG PS = 0 or 1, predominate clear cell histology	592	OS, DFS, toxicity
PROTECT	NCT0135962	Completed	Pazopanib	Industry; GSK	MC, DB, R, PC	11/2010 04/2017	Modified UISS, Karnofsky performance scale of at least 80, clear cell or predominate clear cell histology	1500	Primary endpoint DFS not met
SORCE	NCT0092258	Completed	Sorafenib	Medical Research Council UK	MC, DB, R, PC	05/2007 2013	Intermediate- and high-risk SSIGN, ECOG PS = 0 or 1, clear or non-clear cell RCC	1656	OS, DFS, toxicity, QoL
SWOG-S0931	NCT0120249	Active, not recruiting	Everolimus	NIH, SWOG, NCI	MC, DB, R, PC	04/2011	Pathological high or very high risk, no further details available, ECOG PS = 0 or 1	1218	RFS, OS toxicity

Table 3-1: Clinical Trials Database Listed Large, Multicenter, Placebo-Controlled, Randomized, Double-blind, Adjuvant Clinical Trials in RCC (Completed)

Acronym	Trial No.	Status	Intervention	Funding Body/ Sponsors	Design	Start Date/ Est Complete Date	Stratification	Estimated Enrollment	Outcome Measures
S-TRAC	NCT00375674	Completed	Sunitinib	Industry, Pfizer	PC, DB, R, DB	07/2007 06/2017	High-risk UISS, ECOG PS = 0-2, predominate clear cell histology	720	Primary endpoint DFS met per IRC not met per investigator. OS (immature)

ARISER, Adjuvant Rencarex Immunotherapy Phase III trial to Study Efficacy in non-metastatic RCC[8]; ASSURE, Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; ATLAS, Adjuvant Axitinib[9] Treatment of Renal Cancer: A Randomized Double-blind Phase 3 Study of Adjuvant Axitinib v Placebo in Subjects at High Risk of Recurrent RCC; PROTECT, a Randomized, Double-blind, Placebo-controlled Phase III Study to Evaluate the Efficacy and Safety of Pazopanib as Adjuvant Therapy for Subjects with Localized or Locally Advanced RCC Following Nephrectomy; SORCE, a Phase III Randomized, Double-blind Study Comparing Sorafenib with Placebo in Patients with Resected Primary Renal Cell Carcinoma at High or Intermediate Risk of Recurrence; S-TRAC, Sunitinib Treatment of Renal Adjuvant Cancer: A Randomized Double-blind Phase 3 Study of Adjuvant Suntinib v Placebo in Subjects at High Risk of Recurrent RCC[10]; SWOG-S0931, EVEREST, EVErolimus for Renal Cancer Ensuring Surgical Therapy, a Phase III Study.

DB, Double-blind; ECOG, Eastern Cooperative Group; DFS, Disease-free survival; PS, performance score; MC, multicenter; NCI, National Cancer Institute; NIH, National Institute of Health; OL, open-label; OS, overall survival; PC, placebo-controlled; QoL, quality of life; SWOG, Southwest Oncology Group; R, randomized; TN, tumor, node; UISS, UCLA Integrated Staging System

The first trial to report results, ECOG 2805 (ASSURE), revealed no benefit in disease-free survival (DFS) after 1 year of adjuvant sunitinib or sorafenib versus placebo.[11] Median DFS was 5.8 years (IQR, 1.6−8.2) for sunitinib (hazard ratio [HR] 1.02, 97.5% CI 0.85–1.23, P = 0.8038), 6.1 years (IQR, 1.7–not estimable [NE]) for sorafenib (HR 0.97, 97.5% CI 0.80–1.17, P=0.7184), and 6.6 years (IQR, 1.5–NE) for placebo. The most common Grade 3 or worse AEs were hypertension (105 [17%] participants on sunitinib and 102 [16%] participants on sorafenib), hand-foot syndrome (94 [15%] participants on sunitinib and 208 [33%] participants on sorafenib), rash (15 [2%] participants on sunitinib and 95 [15%] participants on sorafenib), and fatigue (110 [18%] participants on sunitinib and 44 [7%] participants on sorafenib). Reduced doses of sunitinib still resulted in high toxicity.

In the Phase III PROTECT trial, 1538 participants with completely resected RCC were randomly assigned to pazopanib or placebo for 1 year. The starting dose of pazopanib was reduced from 800 to 600 mg daily, after enrollment of 403 participants, due to high rates of treatment discontinuations due to excess risk of hepatotoxicity. After median follow-up of approximately 60 months, DFS for those treated with 600 mg/day dosing was not statistically different between pazopanib and placebo (67 versus 64 percent three-year DFS, HR 0.94, 95% CI 0.77-1.14). However, DFS was improved for those assigned to 800 mg/day dosing (66 versus 56 percent, HR 0.66, 95% CI 0.49-0.90). Overall survival, a secondary endpoint, was immature.[12]

In a Phase III randomized, double-blind, placebo-controlled trial (ATLAS) conducted in 724 participants with localized RCC status postnephrectomy, axitinib 5 mg oral twice daily, failed to demonstrate a DFS advantage in the total study population. There was no significant difference in DFS per independent review committee assessment in the intention-to-treat population (HR 0.870, 95% CI 0.660–1.147; p 0.3211) or per investigator assessment (HR 0.776, 95% CI 0.599–1.005; P = 0.0536).Overall survival data were not mature. Grade 3 or greater toxicities were more frequent in the axitinib arm (61 versus 30 percent).[13]

Another large Phase III trial, ARISER, a double-blind, placebo-controlled study, evaluated girentuximab (an antibody targeting carbonic anhydrase IX). Co-primary endpoints were DFS and OS assessed by independent radiologic review. No statistically significant DFS (HR = 0.97; 95% CI 0.79–1.18) or OS (HR = 0.99; 95% CI 0.74–1.32) benefit was observed. [14]

In SORCE, a Phase III study comparing sorafenib 400 mg twice daily for 3 years, sorafenib 400 mg twice daily for 1 year followed by placebo for 2 years, and placebo for 3 years. Participants were randomized in a 3:3:2 fashion. This study targeted intermediate- or high-risk disease by Leibovich score and allows both clear cell and non-clear cell histologies. The initial sorafenib dose was 400 mg twice per day orally, amended during trial recruitment to a reduced starting dose of 400 mg daily. The primary outcome was investigator-reported DFS. There were no differences in DFS or OS for all randomized participants, high-risk participants only, and participants with only clear cell RCC. Median DFS was not reached for three years of sorafenib or for placebo (HR= 1.01, 95% CI 0.82 -1.23, P = 0.946). The mean DFS was 6.81 years for three years of sorafenib and 6.82 years for placebo, a difference of 0.01 (95% CI 0.49 – 0.48, P = 0.99).[15]

Recently, the S-TRAC study was reported to have met its primary endpoint of improved DFS by blinded independent central review (BICR) for sunitinib vs placebo. The population targeted in the study was predominantly clear cell and had a diagnosis of locoregional RCC (tumor stage 3 or higher, regional lymph-node metastasis or both) on the basis of modified UISS criteria. The median DFS was 6.8 years (95% CI, 5.8 to NR) vs 5.6 years (95% CI, 3.8 to 6.6), (HR = 0.76, 95% CI, 0.59-0.98, P = 0.03). Of note, investigator-assessed DFS did not show any statistical difference between sunitinib and placebo. Overall survival (OS) data were not mature at the time of data cutoff. Dose reductions because of AEs were more frequent in the sunitinib group than in the placebo group (34.3% vs 2%), as were dose interruptions (46.4% vs 13.2%) and discontinuations (28.1% vs 5.6%). Grade 3 or 4 AEs were more frequent in the sunitinib group (48.4% for Grade 3 events and 12.1% for Grade 4 events) than in the placebo group (15.8% and 3.6%, respectively). There was a similar incidence of serious adverse events (SAEs) in the 2 groups (21.9% for sunitinib vs 17.1% for placebo). No deaths were attributed to toxic effects. From a quality of life prospective, participants in the sunitinib arm had lower scores (EQ-5D and QLC-C30) than the placebo group, reaching clinically significant differences for diarrhea and loss of appetite.[10]

Based on the above results, sunitinib (50 mg daily 4 weeks on, 2 weeks off, for 1 year) was approved in the United States as adjuvant therapy following nephrectomy for participants at high risk of relapse. Although improved DFS findings per BICR were noted in the S-TRAC study, there was an absence of DFS improvement based on investigator assessment, immature OS finding, a need for frequent dose adjustments, and interruptions to manage sunitinib-related toxicities, and an overall decrease in quality of life of participants on sunitinib. National Cancer Comprehensive Network (NCCN) guidelines have been updated and indicate for RCC clear cell histology and high risk; clinical trial (preferred) or surveillance or adjuvant sunitinib (category 2B).[16]

In conclusion, at this time, surgery for primary tumors remains the best chance to cure patients with localized RCC. However, survival rates in higher risk patients remain poor, and novel therapeutic approaches are needed to improve prognosis in these patients.

3.1 Study Rationale

Encouraging results have been observed in both treatment-experienced and treatment-naive advanced RCC participants who received either nivolumab monotherapy or nivolumab plus ipilimumab (Section 3.2.1). Therefore, it is rational to continue to evaluate these immunotherapies in the adjuvant setting versus the current RCC standard of care.

With the implementation of this proposed amendment, Part A of the study remains identical to the original protocol design. The addition of Part B to the protocol includes a monotherapy nivolumab arm. A target of approximately 1600 participants are planned (n=800 Part A and n=800 Part B) to be randomized in study CA209914, with the primary endpoint of DFS and secondary endpoints of OS, and safety and tolerability.

The study is designed to demonstrate superiority of the combination of nivolumab and ipilimumab over placebo, and to then demonstrate superiority of monotherapy nivolumab over placebo and to support registration of the combination and monotherapy in adjuvant RCC. The contribution of

components of the combination is planned to be assessed using a contemporaneously enrolled combination and monotherapy subgroup within the CA209914 study.

The original primary endpoint, DFS for the combination treatment compared to the placebo arm is largely unimpacted by Revised Protocol 03. The primary test for participants randomized 1:1 to receive nivolumab + ipilimumab versus placebo will occur as originally planned.

The additional monotherapy arm in Part B, will allow the efficacy assessment by directly evaluating the difference between 200 participants, contemporaneously randomized to nivolumab + ipilimumab versus 400 participants contemporaneously randomized to nivolumab monotherapy.

Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide a risk-benefit assessment of both adjuvant combination therapy and monotherapy.

3.1.1 Research Hypothesis

Treatment with nivolumab combined with ipilimumab compared with placebo infusions and treatment with nivolumab monotherapy compared with placebo infusions, will improve DFS in participants with localized RCC with a predominantly clear cell histology who underwent radical or partial nephrectomy.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab and ipilimumab in combination is provided in the Nivolumab Investigator's Brochure (IB).

3.2.1 Indication Background

3.2.1.1 Nivolumab Monotherapy in RCC

Harnessing the immune system would be an attractive opportunity, together with efforts to find cell surface markers that can be used to trace and target dormant renal-cell carcinoma cells. Nivolumab monotherapy has been studied in participants with advanced RCC in several BMS-sponsored studies (Phase 1 through 3): MDX1106-03, CA209009, CA209010, and CA209025. MDX1106-03 was a Phase I refractory solid tumor trial, which included 34 participants with previously-treated advanced RCC who received nivolumab at 1 mg/kg (n = 18) or 10 mg/kg (n = 16) given every 2 weeks.[17,18,19] In both the 1 mg/kg and 10 mg/kg cohorts, approximately 30% of participants experienced an objective response with median duration of response of 12.9 months. Responses were generally rapid with a median time to response of 16 weeks. Notably, responses could occur after treatment cessation and persist off treatment. Median progression-free survival (PFS) was 7.3 months. Median overall survival (mOS) was 22.4 months. These results were promising given that many of the participants were heavily pre-treated with 71% having had 2 or more lines of therapy. Treatment-related AEs of any grade were observed in 85% of RCC participants; the most common were fatigue (41%), rash (27%), diarrhea (18%), and pruritis (18%). Grade 3-4 treatment-related AEs were observed in 18% of RCC participants. The spectrum, frequency, and severity of treatment-related AEs were similar in the RCC population compared to the overall study population and were similar across dose levels.

In order to identify a potential dose-response relationship in RCC, a randomized Phase 2 study (CA209010) was conducted in 168 participants with advanced RCC previously treated with an antiangiogenic therapy who received nivolumab at 0.3 mg (n = 60), 2 mg/kg (n = 24) or 10 mg/kg (n=54) given every 3 weeks.[18] No dose response relationship was found as measured by PFS, with median PFS of 2.7, 4.0, and 4.2 months for the 0.3, 2, and 10 mg/kg groups, respectively (P = 0.9). Objective response rate (ORR) was 20%, 22%, and 20% in the 0.3, 2, and 10 mg/kg groups, respectively. Median time to achievement of an objective response was 2.8-3.0 months. The median duration of response was 22.3 months (4.8, NR) in the 10 mg/kg arm and not yet reached in the 2 lower dose cohorts. Median OS was at 18.2 to 25.5 months, with a minimum of follow-up of 24 months. Fatigue was the most frequent toxicity (22-35%). No new toxicities were identified with 11% experiencing Grade 3-4 treatment-related AEs, none of which were due to pneumonitis. Treatment-related AEs led to discontinuation of study drug in 7% of participants.

A parallel biomarker-focused trial, CA209009, using the same 3 nivolumab dose levels (0.3, 2, and 10 mg/kg every 3 weeks) was executed to explore predictors of response and identify mechanisms of resistance.[20] This study included 67 participants with previously-treated, advanced RCC who were randomized to one of the 3 nivolumab dose groups and 24 participants with previously-untreated RCC who received nivolumab at 10 mg/kg every 3 weeks. The results mirrored the efficacy and toxicity profile of CA209010, with an ORR of 18% in previously-treated participants, and 13% in previously untreated participants and disease stabilization in another 32% of previously treated and untreated participants. At 24 weeks, 36% of participants were free from progression. Of 56 participants with evaluable pretreatment tumor samples, 18 (32%) had ≥ 5% PD-L1 tumor expression. ORR was 22% among those with ≥ 5% PD-L1 tumor expression versus 8% among those with < 5% PD-L1 tumor expression.

Based on the clinical activity of nivolumab observed in these Phase 1 and 2 studies, a large Phase 3 trial (CA209025) was conducted in 821 participants with advanced RCC previously treated with 1 or 2 antiangiogenic therapies who were randomized to receive nivolumab 3 mg/kg every 2 weeks or everolimus 10 mg daily. A planned interim analysis, after a minimum of follow-up of 14 months, demonstrated a statistically significant and clinically meaningful improvement in OS of nivolumab monotherapy vs everolimus (median OS, 25.0 months vs 19.6 months, respectively; HR 0.73 [98.5% CI, 0.57 to 0.93] P = 0.002). ORR was 25% for nivolumab vs 5% for everolimus. Additional efficacy results are presented in Table 3.2.1.1-1. Among 756 participants with quantifiable PD-L1 tumor expression in pretreatment samples, 24% had ≥1% PD-L1 expression. Among participants with ≥ 1% PD-L1 expression, median OS was 21.8 months in the nivolumab group and 18.8 months in the everolimus group (HR, 0.79; 95% CI, 0.53 to 1.17). Among participants with < 1% PD-L1 expression, the median OS was 27.4 months in the nivolumab group and 21.2 months in the everolimus group (HR, 0.77; 95% CI 0.60 to 0.97). No new safety concerns were identified, and nivolumab monotherapy showed a favorable safety profile as compared to everolimus, evidenced by the lower rates of drug-related AEs (all grades, 79% vs 88%; Grade 3-4, 19% vs 37%, respectively) and drug-related AEs leading to discontinuation (all grades, 8% vs 13%, respectively) in the nivolumab group. These results were the basis for regulatory approval of nivolumab monotherapy in advanced RCC.

Single agent activity and tolerability of anti-PD1 in the first line metastatic setting further supports the evaluation of nivolumab monotherapy in the adjuvant setting. In the phase 2, nonrandomized, noncomparative, KEYNOTE-427[21] study, pembrolizumab was studied as monotherapy in 110 participants with advanced clear cell RCC who had not received prior systemic therapy, including 41 IMDC favorable-risk participants. The interim data showed single-agent activity with an overall response rate of 38.2% including a CR rate of 2.7%. Responses lasting for 6 months or more were observed in 74.8% of participants. The median PFS was 8.7 months (95% CI: 6.7-12.2 months) and the 6 month PFS rate was 60.2%. In an analysis based on PD-L1 status, participants whose tumors expressed PD-L1 (combined positive score [CPS] ≥ 1) (n = 46) had an ORR of 50.0% (95% CI: 34.9–65.1), with a CR rate of 6.5%. In participants whose tumors did not express PD-L1 (CPS < 1) (n = 53), ORR was 26.4% (95% CI: 15.3–40.3) (all responses were PRs).

TITAN-RCC provided support to the added value of ipilimumab in combination with nivolumab in advanced renal cell carcinoma. In the phase 2 TITAN-RCC[22] study (0216-ASG), open-label nivolumab was initiated as monotherapy and an "immunotherapeutic boost" of nivolumab plus ipilimumab was given only to nonresponders. The study enrolled 207 previously untreated and pretreated (2nd line), advanced or metastatic renal cell carcinoma (mRCC) subjects with intermediate and high risk disease according to IMDC.

Participants were treated first-line (n = 108) or second-line (after a TKI, n = 99) with nivolumab 240 mg given every 2 weeks as induction therapy. Those with early significant progressive disease by week 8 or either stable or progressive disease at week 16 received 2 to 4 boost cycles of nivolumab plus ipilimumab. Those who did not respond to the boosts were considered immunotherapy resistant. Partial (PR) and complete responders (CR) to nivolumab monotherapy continued with nivolumab maintenance therapy, with combination therapy added only if they began to progress.

Confirmed ORR with first-line nivolumab monotherapy at 16 weeks was 28.7% (95% confidence interval 20–38). Boosting improved ORR to 37% (95% confidence interval 28–47). In the second-line setting it was 18.2%. Boosting improved ORR to 28.3% (95% confidence interval 20-8).

In the first-line setting, improvement in BOR with the addition of boost therapy was 29.8%. In the second-line setting it was 38.6%.

Discontinuation due grade 3 or 4 adverse events was 14% in the first-line and 20% in the second-line setting.

Table 3.2.1.1-1: Summary of Efficacy Results - All Randomized Subjects - CA209025

Efficacy Parameters	Nivolumab (N = 410)	Everolimus (N = 411)
Primary Endpoint		
Overall Survival		
Events, n (%)	183/410 (44.6)	215/411 (52.3)
Stratified log-rank test P value[a,b]	0.0018	
HR (98.52% CI)[c]	0.73 (0.57, 0.93)	
Median OS (95% CI), months[d]	25.00 (21.75, NR)	19.55 (17.64, 23.06)
OS Rate at 6 months (95% CI), %[d]	89.2 (85.7, 91.8)	81.2 (77.0, 84.7)
OS Rate at 12 months (95% CI), %[d]	76.0 (71.5, 79.9)	66.7 (61.8, 71.0)
Secondary Endpoints		
Objective Response Rate per Investigator (CR + PR)[e]		
N (%)	103 (25.1)	22 (5.4)
95% CI[f]	(21.0, 29.6)	(3.4, 8.0)
Odds ratio estimate (95% CI)[g,h]	5.98 (3.68, 9.72)	
P Value[i]	< 0.0001	
Duration of response[e]		
Ongoing responders, n/N (%)	49/103 (47.6)	10/22 (45.5)
Median (95% CI), months[d]	11.99 (7.85, 23.03)	11.99 (6.44, NR)
Min, Max[j]	0.0, 27.6+	0.0+, 22.2+
Progression-free survival		
Events, n (%)	318 (77.6)	322 (78.3)
Stratified log-rank test p value[a]	0.1135	
HR (95% CI)[c]	0.88 (0.75, 1.03)	
Median 95% CI)	4.60 (3.71, 5.39)	4.44 (3.71, 5.52)

[a] Log-rank test stratified by the MSKCC risk group (poor vs intermediate vs favorable), the number of prior antiangiogenic therapies in the advanced/metastatic setting (1 vs 2), and the region (W. Europe, US/Canada vs Rest of the World) as entered into the IVRS.

[b] Based on the 398 observed deaths and O'Brien-Fleming alpha spending function, the boundary for statistical significance requires the P value to be less than 0.0148.

[c] Stratified Cox proportional hazard model. Hazard ratio is nivolumab over everolimus.

[d] Based on Kaplan-Meier Estimates.

[e] The confirmed ORR was 88/410 (21.5%) in the nivolumab group and 16/411 (3.9%) in the everolimus group (stratified CMH test P value < 0.0001), with a median DOR of 23.03 months in the nivolumab group and 13.73 months in the everolimus group.

[f] CR+PR, confidence interval based on the Clopper and Pearson method.

[g] Cochran-Mantel-Haenzel test stratified by the MSKCC risk group (poor vs intermediate vs favorable), the number of prior anti-angiogenic therapies in the advanced/metastatic setting (X vs 2) and the region (Western Europe vs US/Canada vs Rest of the World) as entered into the IVRS.

[h] Ratio of nivolumab over everolimus

[i] Two-sided p value from CMH test for the comparison of the odds ratio of nivolumab over everolimus.

[j] Symbol + indicated a censored value.

3.2.1.2 Ipilimumab in Renal Cell Carcinoma

Ipilimumab monotherapy for the treatment of mRCC was studied in the Phase 2 clinical trial MDX010-11.[23] Two sequential cohorts were studied, each with a loading dose of 3 mg/kg followed by 3 doses of either 1 mg/kg (group 3-1; n = 21) or 3 mg/kg (group 3-3; n = 40). Participants with stable disease or partial or complete response were allowed additional treatment. In Group 3-1 (n = 21), 1 participant (5%) had a PR.[24] In Group 3-3 (n = 40), 5 participants (12.5%) had a PR. Among 14 treatment-naive participants in Group 3-3, 3 (21%) had a PR.

In the ipilimumab monotherapy Phase 2 clinical trial MDX010-11, the major toxicities were colitis (all Grade 3/4; 14% in Group 3-1, 33% in Group 3-3) and hypophysitis (1 Grade 3/4, 1 Grade 1/2 in Group 3-3; none in Group 3-1). Most reported AEs were Grade 1/2 (57% in Group 3-1, 35% in Group 3-3) or Grade 3 (38% in Group 3-1, 48 % in Group 3-3).[25] The most common treatment-related AEs in Group 3-1 (total 81%) and Group 3-3 (total 93%) were diarrhea (38% and 40%, respectively) and fatigue (33% and 38%, respectively). Most AEs were manageable with appropriate treatment, including high-dose corticosteroids and hormone replacement.

3.2.1.3 Nivolumab Plus Ipilimumab in RCC

Promising safety and efficacy results were also observed with the combination of nivolumab and ipilimumab in the advanced RCC population in study CA209016,[26] a Phase 1 dose-escalation study of nivolumab in combination with VEGFR-TKIs or ipilimumab in participants with metastatic RCC. Treatment-experienced and -naive participants with metastatic RCC 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. In Arm N1+I3, 25 out of 47 participants (53%) were treatment-naive. Approximately 62% were characterized as Intermediate Risk by the Memorial Sloan Kettering Cancer Center (MSKCC) categories, and 4.3% were categorized as Poor Risk. In Arm N3 + I3, 21 of 47 participants (45%) were treatment-naive. Sixty-six percent (66.0%) were classified as Intermediate Risk, and 6.4% were categorized as Poor Risk. The primary objective was to assess safety/tolerability; the secondary objective was to assess antitumor activity.

After a minimum of 22 months, the level of clinical activity, as measured by confirmed ORR, for the combination of nivolumab and ipilimumab in CA209016 was substantially greater than that observed in studies of either nivolumab (Section 3.2.1.1) or ipilimumab monotherapy (Section 3.2.1.2) in metastatic RCC, including in the treatment-naive subpopulation (see Table 3.2.1.3-1). The dosing regimen including nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg (N3 + I1) was chosen for further clinical evaluation because it exhibited similar clinical activity to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg (N1 + I3) but had a more favorable safety profile.

Table 3.2.1.3-1: Antitumor Activity in All Participants (CA209016)

	N3 + I1 (n = 22) Previously Treated	**N3 + I1 (n = 25) Treatment-Naive**	**N1 + I3 (n = 26) Previously Treated**	**N1 + I 3 (n = 21) Treatment-naive**
Confirmed ORR, n (%) (95% CI)	10 (45.5)	9 (36.0) (18.0, 57.5)	10 (38.5)	9 (42.9) (21.8, 66.0)
Median duration of response, weeks (range)	60.1 (9.29, NA)	88.7 (30.00, 105.00)	74.4 (12.29, 108.29)	NR (23.57, NA)
Ongoing responses, % (n/N)	4 (40.0)	4 (44.4)	2 (20.0)	5 (55.6)
Best objective response, n (%)				
Complete response	3 (13.6)	2 (8.0)	0	0
Partial response	7 (31.8)	7 (28.0)	10 (38.5)	9 (42.9)
Stable disease	6 (27.3)	13 (52.0)	11 (42.3)	6 (28.8)
Progressive disease	6 (27.3)	6 (27.3)	3 (11.5)	5 (23.8)
Unable to determine	0	0	2 (7.7)	1 (4.8)
PFS Median months (CI)	6.6 (1.41, 16.39)	8.3 (3.55, 19.29)	10.1 (5.42, 20.76)	8.5 (2.00, NA)
6-month PFS Median months (CI)	54.5 (32.1, 72.4)	8.3 (3.55, 19.29)	65.4 (44.0, 80.3)	61.9 (38.1, 78.8)
Median OS	NR (10.02, NA)	NR (26.68, NA)	30.9 (25.99, NA)	NR (17.45, NA)

NA, not applicable; N,R not reached.

Among the 91 participants treated with the nivolumab + ipilimumab combination in CA209016 who provided evaluable baseline tumor samples, 37.4% had ≥ 1% PD-L1 tumor expression, and 16.5% had ≥ 5% PD-L1 tumor expression. ORR was 47.1% among participants with ≥1% PD-L1

expression and 36.8% among participants with < 1% PD-L1 expression. Among participants with ≥ 5% PD-L1 expression, ORR was 40.0%.

Among all treated participants in the Arms N3 + I1 and N1 + I3, AEs were seen in 43/47 (91.5%) participants in the N3 + I1 arm and 45/47 (95.7%) participants in the N1 + I3 arm. In the N3 + I1 arm, the most frequently reported drug-related AEs were fatigue (51.1%); rash, and pruritus (each 31.9%); nausea (27.7%); arthralgia (25.5%).[28] In the N1 + I3 arm, the most frequently reported drug-related AEs were fatigue (68.1%); diarrhea, and nausea (each 44.7%); pruritus (36.2%); lipase increased (34%); AST increased (31.9%); ALT increased, and decreased appetite (29.8%); hypothyroidism (27.7%); and rash (25.5%).[28]

In the N3 + I1 arm, the most frequently reported, Grade 3-4 drug-related AE was lipase increased (14.9%). In the N1 + I3 arm, the most frequently reported Grade 3-4 drug related AEs were lipase increased (27.7%); ALT increased (21.3%); diarrhea, and colitis (14.9%); AST increased (12.8%).[28]

Treatment-related AEs (including Grade 3-4), treatment-related AEs leading to discontinuation, and treatment-related SAEs all occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm (Table 3.2.1.3-2).

Table 3.2.1.3-2: Summary of Safety Results in Study CA209016 - All Treated Subjects

	Arm I-1 IPI1 + NIV3 N = 47		**Arm I-3 IP13 + NIV1 N = 47**	
Death, n (%)	16 (34.0)		18 (38.3)	
Within 30 Days of Last Dose	0		1 (2.1)	
Within 100 Days of Last Dose	3 (6.4)		4 (8.5)	
Due to Study Drug Toxicity	0		0	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs, n (%)	29 (61.7)	20 (42.6)	30 (63.8)	24 (51.0)
Drug-related SAEs, n (%)	11 (23.4)	9 (19.1)	16 (34.0)	16 (34.0)
All-causality AEs Leading to Discontinuation, n (%)	5 (10.6)	3 (6.4)	15 (31.9)	11 (23.4)
Drug-related AEs Leading to Discontinuation, n (%)	5 (10.6)	3 (6.4)	13 (27.7)	9 (19.1)
All-causality AEs, n (%)	47 (100.0)	33 (70.2)	47 (100.0)	34 (72.3)
Drug-related AEs, n (%)	43 (91.5)	18 (38.3)	45 (95.7)	29 (61.7)
All-causality Select AEs, within 30 Days of Last Dose, by Category, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Endocrine	14 (29.8)	3 (6.4)	19 (40.4)	0
Gastrointestinal	16 (34.0)	3 (6.4)	25 (53.2)	12 (25.5)
Hepatic	11 (23.4)	3 (6.4)	15 (31.9)	8 (17.0)
Pulmonary	3 (6.4)	0	5 (10.6)	0
Renal	11 (23.4)	2 (4.3)	10 (21.3)	2 (4.3)
Skin	29 (61.7)	1 (2.1)	33 (70.2)	1 (2.1)

Table 3.2.1.3-2: Summary of Safety Results in Study CA209016 - All Treated Subjects

	Arm I-1 IPI1 + NIV3 N = 47		Arm I-3 IP13 + NIV1 N = 47	
Hypersensitivity/Infusion Reactions	5 (10.6)	0	3 (6.4)	0
Drug-related Select AEs, within 30 Days of Last Dose, by Category, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Endocrine	13 (27.7)	2 (4.3)	19 (40.4)	0
Gastrointestinal	12 (25.5)	2 (4.3)	21 (44.7)	11 (23.4)
Hepatic	9 (19.1)	3 (6.4)	13 (27.7)	8 (17.0)
Pulmonary	3 (6.4)	0	5 (10.6)	0
Renal	9 (19.1)	2 (4.3)	6 (12.8)	1 (2.1)
Skin	23 (48.9)	0	28 (59.6)	1 (2.1)
Hypersensitivity/Infusion Reactions	5 (10.6)	0	3 (6.4)	0
All-causality Immune-mediated AEs, by Category				
Immune-mediated AEs Treated with Immune-modulating medication	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Diarrhea/Colitis	3 (6.4)	2 (4.3)	12 (25.5)	10 (21.3)
Hepatitis	5 (10.6)	2 (4.3)	11 (23.4)	8 (17.0)
Pneumonitis	1 (2.1)	0	5 (10.6)	0
Nephritis and Renal Dysfunction	2 (4.3)	1 (2.1)	1 (2.1)	0
Rash	8 (17.0)	1 (2.1)	9 (19.1)	1 (2.1)
Hypersensitivity	0	0	0	0
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Adrenal Insufficiency	3 (6.4)	1 (2.1)	6 (12.8)	0
Hypophysitis	1 (2.1)	1 (2.1)	2 (4.3)	0
Hypothyroidism/Thyroiditis	10 (21.3)	0	14 (29.8)	0
Hyperthyroidism	4 (8.5)	1 (2.1)	8 (17.0)	0
Diabetes Mellitus	0	0	0	0

MedDRA version 18.1; CTC version 4.0. All events are within 100 days of the last dose of study drug, unless otherwise indicated.

Sources: Table S.6.2A (deaths), Table S.6.3A (all-causality SAEs), Table S.6.3B (drug-related SAEs), Table S.6.4B (all-causality AEs leading to discontinuation), Table S.6.4D (drug-related AEs leading to discontinuation), Table S.6.2 (all-causality AEs), Table S.6.3.1 (drug-related AEs), Table S.6.101 (all-causality select AEs), Table S.6.105 (all-causality endocrine select AEs), Table S.6.103 (drug-related select AEs), Table S.6.107 (drug-related endocrine select AEs), Table S.6.202 (all-causality IMAEs with exception of endocrine), and Table S.6.204 (all-causality endocrine IMAEs).

Based on the results from CA209016, a large Phase 3 trial was initiated comparing nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV every 2 weeks vs sunitinib 50 mg orally daily for 4 weeks on, 2 weeks off, in participants with previously untreated advanced or metastatic RCC (CA209214). The co-

primary endpoints were ORR, PFS, and OS in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate and poor-risk participants. Overall, alpha of 0.05 was split among the co-primary endpoints (0.001 for ORR, 0.009 for PFS, and 0.04 for OS). ORR, PFS, and OS in all randomized participants (including all IMDC risk groups) were secondary endpoints.

There were 550 participants randomized to nivolumab + ipilimumab (including 425 participants with intermediate/poor risk) and 546 participants randomized to sunitinib (including 422 participants with intermediate/poor risk). The study was stopped early based on the independent data monitoring committee recommendation after reviewing the results of the planned interim analysis of OS (at a median follow-up of 25.2 months), which demonstrated a 37% reduction in the risk of death for intermediate/poor risk participants in the nivolumab + ipilimumab group compared to those in the sunitinib group. The combination of nivolumab with ipilimumab also met the co-primary endpoint of ORR in intermediate/poor risk participants, yielding an ORR of 42% vs 27% in the sunitinib arm. A clinically meaningful improvement in PFS was also demonstrated with the nivolumab + ipilimumab combination vs sunitinib. Detailed information is presented in Table 3.2.1.3-3.

Table 3.2.1.3-3: CA209-214 Overall Survival, Objective Response, Best Overall, and Duration of Response (Intermediate/Poor Risk)

	Nivo + Ipi (N = 425)	**Sunitinib (N = 422)**
Overall survival (OS) Months (95% CI)	NR (28.2 -NE)	26.0 (22.1 -NE)
	Hazard ratio (99.8% CI), 0.63 (0.44–0.89) $P < 0.0001$	
Confirmed objective response rate (ORR)[a] % (95% CI)	42 (37-47)	27 (22-31)
	P <0.0001	
Confirmed best overall response (BOR)[a], %		
Complete response	9	1
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine / not reported	8	12
Duration of response (DOR) Months (95% CI)	NR (21.8 -NE)	18.2 (14.8 - NE)

NE, not estimable; NR, not reached.

Source: ESMO Congress 2017

[a] Immune-related Response Criteria (irRC)-assessed ORR and BOR by RECIST v1.1

Among all treated participants, treatment-related AEs were seen in 93% (46% Grade 3/4) participants in the nivolumab + ipilimumab arm and 97% (63% Grade 3/4) participants in the sunitinib arm. In the nivolumab + ipilimumab arm, the most frequently reported treatment-

related AEs were fatigue (37%), pruritus (28%), and diarrhea (27%). In the sunitinib arm, the most frequently reported treatment-related AEs were diarrhea (52%); fatigue (49%); hypertension (40%); hand-foot syndrome (43%); nausea (38%); and stomatitis and mucosal inflammation (each 28%).[24,25]

For all treated participants, treatment-related AEs leading to discontinuation occurred in 22% and 12%, and treatment-related deaths occurred in 7 and 4 subjects for the nivolumab + ipilimumab combination and sunitinib arms, respectively. Detailed information is presented in Table 3.2.1.3-4.

Table 3.2.1.3-4: CA209-214 Treatment-Related Adverse Events: All Treated Participants

	NIVO + IPI N = 547		SUN N = 535	
Treatment-related event %	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4[a]**
AEs in ≥ 25% of participants	93	46	97	63
Fatigue	37	4	49	9
Pruritus	28	< 1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	< 1	25	< 1
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	< 1
Stomatitis	4	0	28	3
Hypertension	2	< 1	40	16
Mucosal inflammation	2	0	28	3
Hand-foot syndrome	1	0	43	9
AEs leading to discontinuation, %	22		12	
Deaths	n = 7[b]		n =4[c]	

Source: ESMO Congress 2017

[a] Two participants had grade 5 cardiac arrest.

[b] Pneumonitis, immune-mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection.

[c] Cardiac arrest (n = 2), heart failure, multiple organ failure.

CA209214 demonstrated that the combination of nivolumab + ipilimumab yielded significant improvements in ORR and OS in intermediate/poor-risk treatment-naive advanced RCC compared to sunitinib. The safety profile of nivolumab + ipilimumab was manageable and consistent with previous studies, supporting the use of the combination as a new standard of care option in this

population.[24,25,27] A recent publication also reports the finding of nivolumab plus ipilimumab leading to fewer symptoms and better HRQoL than sunitinib in participants at intermediate or poor risk with advanced renal cell carcinoma.

3.2.2 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.[28,29,30] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[31] 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.[32] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also has 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.[33] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV restimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[34]

3.2.3 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.[35] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.3 Benefit/Risk Assessment

The current standard treatment for early stage (I-III) renal cell cancer (RCC) is surgery. While the prognosis of stage I tumors is excellent, stage II and stage III have a high risk of recurrence and represent a high unmet medical need.

The potential benefit of adjuvant nivolumab plus ipilimumab over standard-of-care (observation) after nephrectomy in early stage RCC is not yet known.

Nivolumab in combination with ipilimumab in CA209214 study has demonstrated significant clinical benefits with reversible and manageable toxicities that are consistent with the known IMAE profile of anti-PD-1 immune therapies. The magnitude of OS benefit from the combination is unprecedented in studies of mRCC for intermediate- and poor-risk participants. Addition of ipilimumab to nivolumab as a combination regimen is expected to show an improvement of PFS over nivolumab monotherapy with a manageable increase in IMAEs. However, emerging data are providing evidence of clinical efficacy using single agent checkpoint therapy in 1L advanced clear cell RCC with the benefit of reduced frequency of IMAEs.[36],[37] These results suggests the potential for improved clinical outcomes also in the adjuvant setting.

The use of ipilimumab 1 mg/kg with a lower frequency of administration (ie, Q6W) in combination with nivolumab has been found to result in improved safety as well as efficacy compared to the N3 + I1 dosing schedule in a Phase 1 study in previously untreated advanced NSCLC (CA209012). Incorporating a dose of 1 mg/kg Q6W ipilimumab into the combination regimen in the RCC adjuvant setting is expected to optimize the safety profile of the combination, without impacting the overall efficacy of the combination. Further justification of the dose can be found in Section 5.5.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies.[26] The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used (Section 3.2.1). Overall, the safety profile of nivolumab in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials. Most AEs are low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of nivolumab and ipilimumab may be found in the Nivolumab IB and will not be repeated herein.

In Part B of the study, a nivolumab monotherapy arm of 240 mg Q2W will be included to evaluate its impact on DFS compared to placebo and the contribution of ipilimumab to efficacy and safety.

In the US, nivolumab is approved at 240 mg Q2W for several different tumor types including the treatment of participants with unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic NSCLC, and advanced RCC. Incorporating a flat 240 mg dose of nivolumab into the monotherapy and combination regimens in the RCC adjuvant setting is expected to simplify treatment with nivolumab monotherapy without impacting the overall safety profile of the combination. The detailed rationale for the use of a flat 240 mg dose of nivolumab is provided in Section 5.5.

Therefore this study will allow a direct evaluation of the benefits and risks of combined nivolumab with ipilimumab and nivolumab monotherapy. In addition, clinical and biological parameters (biomarkers) will be explored to assess whether the risks and benefits are altered within specific risk subgroups.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • Part A: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC, with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab versus placebo infusions in participants with localized renal cell carcinoma, with a predominantly clear cell histology who have undergone nephrectomy.	The primary endpoint is DFS. The primary endpoint of DFS will be programmatically determined based on the disease recurrence date provided by BICR. DFS is defined as the time from randomization to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary renal [RCC] primary cancer), distant metastasis, or death, whichever came first. See Table 10.3.1-1 for censoring rules.
Secondary • Part A: To compare OS, including the 5-year OS rates, of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To compare overall survival (OS), including the 5-year OS rates, of nivolumab versus placebo infusions in participants with localized renal cell	• OS, defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the participants was known to be alive.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
carcinoma with a predominantly clear cell histology who have undergone a nephrectomy. • Part B: To evaluate differences in disease-free survival (DFS) per Blinded Independent Central Review (BICR) and overall survival (OS) of contemporaneously randomized nivolumab combined with ipilimumab participants versus nivolumab participants with localized renal cell carcinoma, with a predominantly clear cell histology, who have undergone a nephrectomy.	• DFS and OS in contemporaneously randomized combination and monotherapy participants.
• To describe the safety and tolerability of nivolumab combined with ipilimumab and nivolumab monotherapy up to 30 and 100 days of last dose of study therapy.	• Safety and tolerability endpoint: type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0], timing, seriousness, and relatedness, and laboratory abnormalities up to 30 and 100 days of last dose of study therapy in all treated participants.
Tertiary/Exploratory • **To assess PFS2 (progression after recurrence)** in participants with localized renal cell carcinoma with a predominantly clear cell histology who have undergone a nephrectomy.	• PFS2.
• To assess efficacy in the high and moderate risk subgroups.	• DFS and OS by the high and moderate risk subgroups.
• To assess disease-related symptoms in each arm based on the National Cancer Comprehensive Network (NCCN) Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19).	• Change in FKSI-19 subscale and total scores relative to baseline.
• To assess changes in global health status in each treatment arm based on EuroQoL's EQ-5D-3L.	• Change in scores from baseline in EQ-5D-3L in both the visual analog scale and the utility index.
• To correlate the primary tumor's expression of PD-L1 with efficacy outcome (DFS, OS).	• DFS and OS as described above.
• Assess association between PD-L1 status and DFS and OS.	• Selected biomarkers.
• To analyze biomarkers in tumor and peripheral blood to evaluate association with clinical efficacy or incidence of adverse events.	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To assess the association between the gene signature recurrence score with efficacy outcomes (DFS, OS).	• Gene-signature based recurrence score and its relationship with efficacy endpoints.
• To characterize the pharmacokinetics of nivolumab and ipilimumab and explore exposure response relationships with respect to safety and efficacy, if applicable.	• Population PK parameters, exposure-response relationship between select PK measures of exposure and safety and efficacy endpoints, if applicable.
• To characterize the immunogenicity of the combination of nivolumab and ipilimumab and nivolumab monotherapy.	• Incidence of anti-nivolumab and anti-ipilimumab antibodies and their potential relationship with safety and efficacy endpoints.
• To assess the impact of SARS-CoV-2 serologic status on participants receiving the combination of nivolumab and ipilimumab or nivolumab monotherapy in the adjuvant setting for RCC [redacted]	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG), from serum samples collected at C1D1, C12D1, follow-up visit 2 and upon occurrence of SARS-CoV-2 infection-related events and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarkers.
• To describe the safety of nivolumab combined with ipilimumab and nivolumab monotherapy beyond 100 days and up to 1 year of last dose of study therapy.	• Safety endpoint: type, incidence, severity (graded by the NCI CTCAE, Version 4.0), timing, seriousness, and relatedness beyond 100 days and up to 1 year of last dose of study therapy in all treated participants.

5 STUDY DESIGN

5.1 Overall Design

The original study design (Part A) is a double-blind, randomized trial of the nivolumab and ipilimumab combination therapy versus placebo infusions in participants with early stage localized RCC with a predominantly clear cell histology who underwent radical or partial nephrectomy. Approximately 1000 participants will be screened, and approximately 800 participants will be randomized.

At the implementation of Revised Protocol 03, Part A of the study remains identical to the original protocol design. The addition of Part B to the protocol includes a monotherapy nivolumab arm. A target of approximately 800 participants are planned to be randomized between 3 arms in a 1:1:2 ratio in Part B, with the primary endpoint of DFS and secondary endpoints of OS, and safety and tolerability.

Approximately 1600 participants in total are expected to be randomized in this study.

Participants will be stratified by pathology according to TNM staging per AJCC staging version 2010 and Fuhrman nuclear grading categories (described below) and by type of nephrectomy procedure (partial versus radical).

TNM staging will be stratified according to the following characteristics:

- pT2a, G3 or G4, N0, M0 and pT2b, G any, N0, M0
- pT3, G any, N0, M0
- pT4, G any, N0, M0 and pT any, G any, N1, M0

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

Figure 5.1-1: CA209914 Part A Study Design Schematic

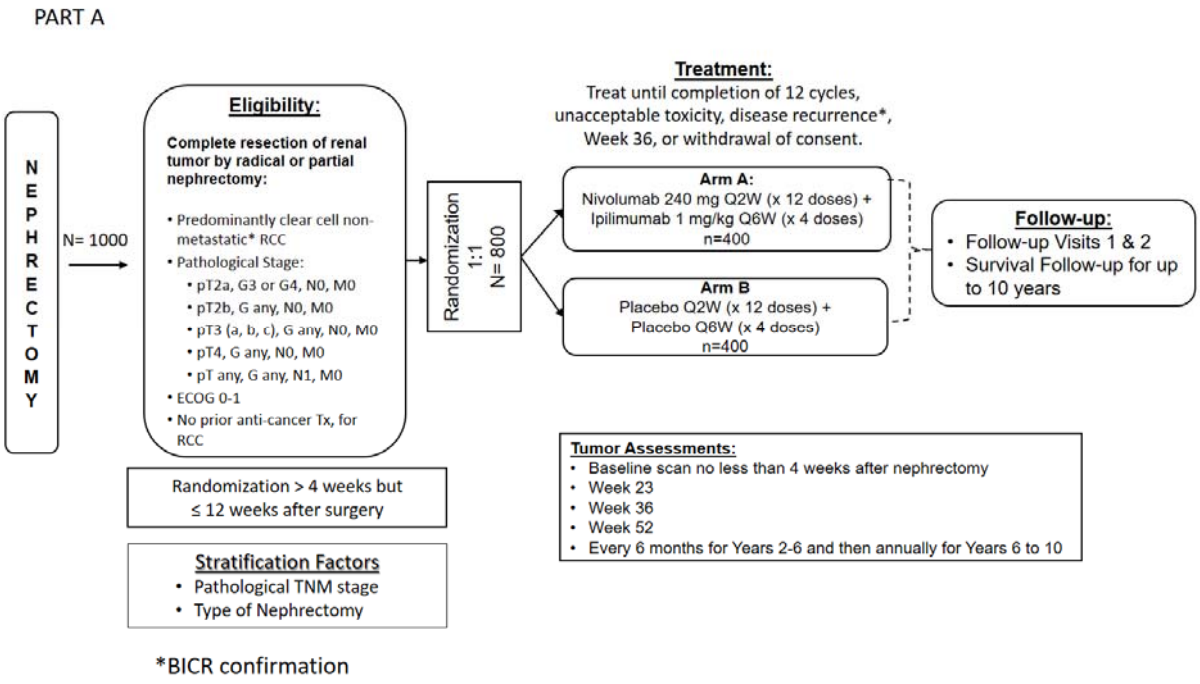
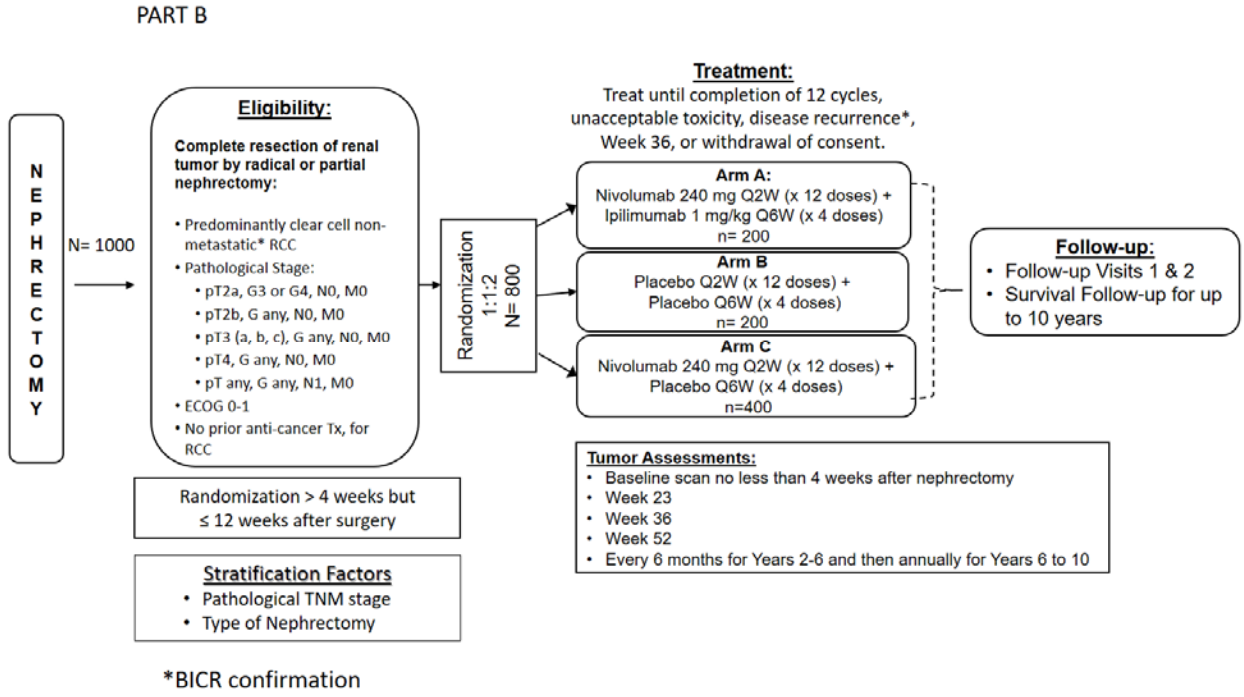


Figure 5.1-2: CA209914 Part B Study Design Schematic



Screening Phase

Screening begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). Randomization must occur greater than 4 weeks and less than (or equal to) 12 weeks from the date of nephrectomy.

Tumor tissue obtained within 3 months prior to enrollment, preferably at the time of the nephrectomy, must be provided for biomarker analyses. Formal infixed, paraffin-embedded- (FFPE) tumor blocks or unstained slides are required for study assessment. Local histopathology review and confirmation of eligibility is required for randomization.

Screening/baseline imaging should be performed at least 4 weeks post-nephrectomy- and submitted to the radiology vendor for BICR confirmation of disease-free status. Pre-nephrectomy images are also requested, if available. Participant eligibility must be confirmed by BICR prior to randomization and will be based only on the review of the baseline scans (and pre-nephrectomy scans if available). As a result, pre-nephrectomy scans, if available, and baseline scans are encouraged to be submitted to BICR within 8 weeks of the nephrectomy to allow for timely return of the decision from the BICR.

During the Screening Phase, laboratory and other tests may be repeated as needed. The most current result prior to randomization is the value by which study inclusion will be assessed (see Section 6.4.1).

The Screening Phase ends with either confirmation of full eligibility and randomization for the participant or with the confirmation that the participant is a screen failure.

Treatment Phase (Part A)

The Treatment Phase begins when the randomization call is made into the IRT. The participant is randomly assigned to 1 of the 2 treatment arms:

- Arm A: Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions

Note: Study treatment must begin within 3 calendar days of randomization.

Treatment Phase (Part B):

The Treatment Phase begins when the randomization call is made into the IRT. The participant is randomly assigned to 1 of the 3 treatment arms:

- Arm A: Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
- Arm B: Placebo infusions at the same frequency of nivolumab and ipilimumab infusions
- Arm C: Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed)
- **Note:** Study treatment must begin within 3 calendar days of randomization.

Randomization can occur once IRT has received confirmation of eligibility from BICR. Each cycle will be 2 weeks (14 days). Participants will receive study drug until the end of 12 cycles (12 nivolumab doses and 4 ipilimumab doses), recurrence, unacceptable toxicity, 36 weeks from first dose, or withdrawal of consent, whichever occurs first. The first cycle will be a combination dose. See Table 7.1.1-2 for the dosing schedule. Study drug may be delayed for toxicity (see Section 7.4.1). Treatment must be completed within 36 weeks after the first dose; any cycles not received within 36 weeks after the first dose will be omitted, and the participant will enter the Follow-up Phase.

A negative pregnancy test should be documented within 24 hours prior to the start of the first dose of the investigational product and every 4 weeks thereafter regardless of dosing. On-study laboratory assessments should be drawn within 72 hours prior to dosing and will be assessed at the local laboratory. Results should be reviewed prior to administration of each dose of study drug.

Tumor assessments will occur in accordance with Table 2-2 until recurrence has been identified by the investigator and is confirmed by BICR. Sites should submit all scans to the third-party vendor on a rolling basis, preferably within 7 business days of scan acquisition, and submit any pertinent cytology/pathology results for central review. If recurrence (defined in Section 9.1.1) is assessed by the investigator, the site will inform the radiology vendor so that the BICR assessment of recurrence can be performed. The BICR assessment of recurrence will be completed, and the results provided to the site within 10 business days of receipt of final images and any pertinent pathology results as specified in Section 9.1.3. BICR assessment of recurrence should only be requested upon recurrence diagnosis by the investigator per the criteria specified in Table 9.1.3.2-

1. The first point of contact should be BMS Imaging Operations Lead and BMS Protocol Team if the site (the Investigator) disagrees with BICR results. The site should not contact the central imaging vendor to discuss or request any details of the BICR assessment.

Participants whose recurrence is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated. Investigators are strongly encouraged to wait for BICR confirmation of recurrence prior to breaking the blind and initiating any subsequent therapy. If the investigator feels that the immediate initiation of subsequent therapy is clinically indicated and does not wish to wait for the confirmation of recurrence from the BICR, then the decision to break the blind must be discussed within the BMS Medical Monitor or designee prior to doing so. See Section 7.3 for additional information regarding unblinding.

PK and immunogenicity samples will be collected according to Table 9.5-1. Adverse event assessments should be documented at each clinic visit.

Quality of Life will be assessed using NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) and EuroQoL's EQ-5D-3L. These questionnaires should be completed according to Table 2-2.

The Treatment Phase ends when the participant is discontinued from study therapy.

Follow-up Phase

The Follow-up Phase begins at the completion of 12 cycles, when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy), or 36 weeks after the first dose, whichever comes first. Participants will have 2 follow-up visits (Follow-up 1 and Follow-up 2) for safety. Follow-up 1 will occur within 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up 2 will occur within 100 days (± 7 days) from the last dose of study therapy. Any ongoing treatment-related AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible. The FKSI-19 and EQ-5D-3L will be completed as described in Table 2-3.

Participants who discontinued study treatment without BICR confirmed recurrence will continue to have tumor assessments performed according to the frequency described in Table 2-3, even if new anti-tumor therapy has been initiated prior to receipt of confirmation. If recurrence (defined in Section 9.1.1) is assessed by the investigator, the site will inform the radiology vendor, so that the BICR assessment of recurrence can be performed. Participants whose recurrence is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until BICR confirms recurrence on a subsequent tumor assessment (see Section 9.1.3.3 for additional details).

After the Follow-up 2 Visit, all participants will be followed for OS status every 12 weeks (± 1 week) until death, withdrawal of consent, lost to follow-up, or end of study. Survival status may be ascertained by telephone contact if the participant is unable to return to the site for a visit. If new anti-tumor therapy is initiated for either disease recurrence or a secondary malignancy at

any time during this period, this and all other pertinent data obtained should be recorded on the appropriate Case Report Form (CRF).

5.1.1 Data Monitoring Committee and Other External Committees

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

5.1.1.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209914. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of study participants. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

5.1.1.2 Blinded Independent Central Review

The BICR will review tumor images and pertinent clinical data (cytology/pathology results) in all randomized participants to determine recurrence for the DFS analyses. Details of the BICR responsibilities, procedures, composition, and process will be specified in the BICR charter.

5.2 Number of Participants

Approximately 1600 participants in total (Parts A + B) will be randomized in this study. Approximately 600 participants have been randomized in Part A with approximately 200 more expected to be randomized (Figure 5.1-1). Approximately 800 participants are expected to be randomized in Part B of this study (Figure 5.1-2). Section 10.1 provides additional details.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of trial is defined as the last participant's last study visit or phone call. 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

5.4.1 Rationale for Selection of Participants at Moderate to High Risk of Relapse

The current standard treatment for early stage (I-III) RCC is surgery. While the prognosis of stage I tumors is excellent, stage II and particularly stage III have a high risk of relapse and represent a high unmet medical need. The adjuvant treatment of patients with RCC remains an area of investigation, with patient selection being a key aspect. Several organizations have guidelines for follow-up surveillance of higher-risk disease. The American Urological Association (AUA) stratifies risk of recurrence on the basis of tumor size and nodal status (low risk: pT1 N0 Nx; moderate to high risk: pT2-4N0, Nx, or any stage N+-),[38] while the European Association of Urology (EAU) bases risk on prognostic nomograms rather than TNM stage.[39]

In study CA209914, the primary endpoint, DFS, will be evaluated in participants at moderate to high risk of recurrence as defined by the AUA. This population represents approximately 40% of the localized RCC population who has undergone surgery. Inclusion of this subset of participants for the primary endpoint of the study will allow for potential meaningful differences in efficacy to be detected earlier than if participants at lower risk of recurrence were included. Since approximately 90% of low risk participants will not have recurrence after nephrectomy, their exclusion will also avoid unnecessary treatment in the vast majority of these low risk participants.

Efficacy will also be assessed in the high and moderate risk subgroups by using the following risk staging system:[40]

High risk:

- pT3, G3 or G4, N0M0
- pT4, G any, N0M0
- pT any, G any, N1M0

Moderate risk:

- pT2a, G3 or G4, N0M0
- pT2b, G any, N0M0
- pT3, G1 and G2, N0M0

Efficacy may also be assessed using a score based on stage, size, grade, and necrosis (the SSIGN score)[41] in the intermediate (3-5) and high (≥6) SSIGN score defined groups.[40]

5.4.2 Rationale for 6 Month Treatment Duration

There is no consensus regarding the optimal treatment duration for patients in the adjuvant setting for localized RCC. Historic Phase 3 trials of adjuvant targeted antiangiogenic therapies have continued treatment for 12 months. Because immunotherapy engages the immune system to control the tumor, continuous treatment, as is required with targeted antiangiogenesis agents and cytotoxic therapy, may not be necessary. Accumulating evidence from different clinical trials in different tumor types with nivolumab monotherapy or nivolumab combined with ipilimumab indicates that responses generally occur early, with a median time to response of 2-4 months, and are durable.[42]

In study CA209016, for example, responses in metastatic RCC participants receiving nivolumab 3 mg/kg /ipilimumab 1 mg/kg combination (n=47) occurred within the first 3 months of treatment, and the median duration of response was 88.7 weeks.[43]

Since standard of care in localized RCC is observation post-nephrectomy and to minimize potential toxicity while maintaining expected efficacy, treatment with nivolumab and ipilimumab or placebo in study CA209914 will be given for 24 weeks in absence of disease recurrence or unacceptable toxicity.

5.4.3 Rationale for 30 min Infusion Duration for Nivolumab and Ipilimumab

The current US label for nivolumab is approved for advanced RCC at 240 mg flat dose administered intravenously over 60 minutes every 2 weeks. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration, and nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in CA209153 in participants (n = 322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in participants administered nivolumab over a 30 minute infusion compared with that reported for participants with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

The risk/benefit profile for ipilimumab has primarily been investigated using a 90-minute infusion. Ipilimumab has been administered safely at doses ranging up to 10 mg/kg over these treatment durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. The shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.[44]

Both agents given as single agent are uncommonly associated with infusion reactions: the incidence is less than 1% for ipilimumab[45] and 3% for nivolumab.[26] In the CA209069 study, hypersensitivity/infusion reactions were listed as 3.2% for the combination and 2.2% for ipilimumab. No Grade 3 or Grade 4 hypersensitivity/infusion reactions were observed in either the combination or single agent ipilimumab treatment groups.[46] Participants should be carefully monitored for infusion reactions during nivolumab/ipilimumab administration.

In this study, nivolumab and ipilimumab will each be infused over 30 minutes.

5.4.4 Rationale for Nivolumab Monotherapy

Nivolumab monotherapy was chosen as one of the treatment arms in Part B because of a favorable risk-benefit ratio assessed from 3 studies in participants with mRCC: CA209010, CA209009, and CA209025.

In CA209010, 168 participants who received at least 1 prior anti-angiogenic therapy were randomized to receive nivolumab 0.3 mg/kg (n = 60), 2 mg/kg (n = 54), and 10 mg/kg (n = 54). [18] Median PFS was 2.7 months, 4.0 months, and 4.2 months at 0.3, 2, and 10 mg/kg, respectively. The ORR ranged from 20% to 22% across dose levels. Median OS was 18.2 months at 0.3 mg/kg, but was not yet reached at the 2 highest dose levels.

CA209009 enrolled a similar population to CA209010, but also included 24 participants with treatment-naive RCC. Among treatment-naive participants, all of whom received nivolumab 10 mg/kg Q3W, the ORR was 13% (3/23). CA209010 includes the largest safety database for nivolumab monotherapy in mRCC. All treated participants (n = 167) were included in the safety analyses. Drug-related AEs of any grade occurred in 74.6%, 66.7%, and 77.8% of participants treated at 0.3 mg/kg, 2 mg/kg, and 10 mg/kg, respectively. The most common (≥ 10% in any group) drug-related AEs included fatigue, dry skin, rash, pruritus, arthralgia, nausea, diarrhea, decreased appetite, dry mouth, and hypersensitivity. Grade 3 drug-related AEs occurred in 5.1%, 16.7%, and 13% of participants treated at 0.3 mg/kg, 2 mg/kg, and 10 mg/kg, respectively. Related Grade 3 events in at least 2 participants across dose levels included nausea, (AST)/ALT increased, and anemia. No drug-related Grade 4 or Grade 5 events occurred. No dose-toxicity relationship was identified except for hypersensitivity/infusion reaction, which occurred most frequently in the 10 mg/kg treatment group.

Based on the clinical activity of nivolumab observed in these Phase 1 and 2 studies, a large Phase 3 trial (CA209025) was conducted in 821 participants with advanced RCC previously treated with 1 or 2 anti-angiogenic therapies who were randomized to receive nivolumab 3 mg/kg every 2 weeks (Q2W) or everolimus 10 mg daily. A planned interim analysis, after a minimum follow-up of 14 months, demonstrated a statistically significant and clinically meaningful improvement in OS of nivolumab monotherapy versus everolimus (median OS, 25.0 months vs 19.6 months, respectively; hazard ratio [HR] 0.73 [98.5% confidence interval (CI), 0.57 to 0.93, p-value (P) = 0.002]). ORR was 25% for nivolumab versus 5% for everolimus. Among 756 participants with quantifiable PD-L1 tumor expression in pretreatment samples, 24% had PD-L1 expression ≥ 1%. Among participants with PD-L1 expression ≥ 1%, median OS was 21.8 months in the nivolumab group and 18.8 months in the everolimus group (HR 0.79 [95% CI, 0.53 to 1.17]). Among participants with PD-L1 expression < 1%, the median OS was 27.4 months in the nivolumab group and 21.2 months in the everolimus group (HR, 0.77 [95% CI, 0.60 to 0.97]). No new safety concerns were identified, and nivolumab monotherapy showed a favorable safety profile as compared to everolimus, evidenced by the lower rates of drug-related AEs (all grades, 79% vs 88%; Grade 3-4, 19% vs 37%, respectively) and drug-related AEs leading to discontinuation (all grades, 8% vs 13%, respectively) in the nivolumab group. These results were the basis for regulatory approval of nivolumab monotherapy in advanced RCC.

As the treatment of RCC landscape continues to evolve, accumulative evidence showed a single-agent activity for anti-PD-1 or anti-PD-L1 monotherapy in the 1L treatment of advanced RCC. If this observation is applicable then there could also be the potential for large improvements in DFS in the adjuvant RCC setting.[47],[48],[49]

Based upon the totality of the safety, efficacy, and exposure-response data, a dose of 240 mg Q2W was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk in the monotherapy arm. In addition, by selecting the 240 mg Q2W, we are aligning the same nivolumab dose and schedule as utilized in both the combination arm and the nivolumab monotherapy comparator arm.

For additional information on nivolumab monotherapy in RCC please refer to section 3.2.1.1

5.5 Justification for Dose

There are 4 completed or ongoing studies of nivolumab monotherapy using body weight normalized dosing (mg/kg) in advanced RCC: MDX1106-03, CA209009, CA209010, and CA209025. In study MDX1106-03, previously-treated RCC participants were administered nivolumab monotherapy with 1 or 10 mg/kg Q2W. In studies CA209009 (which included both previously-treated and previously untreated RCC participants) and CA209010 (which included only previously-treated RCC participants), nivolumab doses of 0.3, 2, or 10 mg/kg were given Q3W. As detailed in Section 3.2.1, clinical activity was observed across all nivolumab dose levels in these studies, in both Q2W and Q3W schedules, and in both previously-treated and previously untreated participants.

Nivolumab pharmacokinetics (PK) and exposures of participants in these studies have been characterized by population pharmacokinetics (PPK) analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab in solid tumors. Based on PK modeling and the long half-life (25 days) of nivolumab, the Q2W schedule was subsequently selected for CA209025 and resulted in sustained exposure between treatments. Study CA209025 demonstrated that nivolumab 3 mg/kg Q2W improved OS and had a favorable safety profile compared to everolimus in previously-treated mRCC, leading to regulatory approval in this population (see Section 3.2.1).

Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab, regardless of tumor type. In the US, the 240 mg Q2W flat dose is now approved for the treatment of patients with unresectable or metastatic melanoma (as monotherapy or as maintenance therapy following nivolumab plus ipilimumab regimen), metastatic NSCLC, and advanced RCC.

The PK and safety of nivolumab have been evaluated in the Asian population. The comparison of PK parameters in global and Japanese participants suggests that the PK of nivolumab is similar in these populations. Nivolumab is shown to be safe and well tolerated in Japanese participants. The similar PK and safety profile of nivolumab between global and Japanese participants supports the use of similar dosing in the Asian population as is being used in global clinical studies.

5.5.1 Justification for Dosage in Combination Treatment of Nivolumab and Ipilimumab

The dose and schedule of nivolumab and ipilimumab for this study was selected based on the data observed in the CA209016 study and in the CA209012 study.[50] As was previously mentioned in Section 3.2.1.3, Study CA209016 demonstrated antitumor activity of nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W (N3 + I1 schedule)

with an ORR of 36% in previously-untreated RCC participants, which is higher than the efficacy with either nivolumab monotherapy (CA209009) or ipilimumab monotherapy (MDX010-11). In CA209012, a multi-cohort Phase 1 study in participants with advanced NSCLC, multiple nivolumab and ipilimumab combination schedules were evaluated in order to optimize safety and efficacy. In addition to evaluating the N3 + I1 schedule (identical to that given in CA209016) in 2 cohorts, CA209012 evaluated nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg either given Q6W or given Q12W in 2 other cohorts. Both the ipilimumab Q6W and Q12W cohorts were associated with improved and manageable tolerability compared to the cohort that received the N3 + I1 schedule. Both cohorts demonstrated encouraging efficacy, yielding ORR of 38% to 47%, which is higher than the ORR observed in the nivolumab monotherapy cohort (ORR 23%) or the N3 + I1 cohorts (ORR 20%, combining squamous and non-squamous cohorts) in the same study. The CA209012 study demonstrated activity of the combination of nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W in both PD-L1+ and PD-L1- tumors, coupled with a manageable safety profile, and this combination regimen in being further evaluated in the Phase 3 CA209227 in previously untreated advanced NSCLC.

Given the demonstrated clinical activity of nivolumab monotherapy in advanced RCC from CA209025 and the similar PK, efficacy, and safety of nivolumab 240 mg Q2W to 3 mg/kg Q2W, CA209914 will use a nivolumab flat dose of 240 mg Q2W as the backbone for the combination regimen with ipilimumab. With both ipilimumab 1 mg/kg Q6W and Q12W schedules showing a similar safety and efficacy profile when combined with nivolumab 3 mg/kg Q2W in CA209012, the ipilimumab 1 mg/kg Q6W schedule was chosen to combine with the nivolumab 240 mg backbone to avoid any potential loss of efficacy with less frequent ipilimumab dosing.

5.5.2 Justification for Dose of Nivolumab Monotherapy Treatment in Part B

Nivolumab will be dosed at 240 mg Q2W in the monotherapy arm. Nivolumab is approved in the US and EU for advanced renal cell carcinoma at 240 mg Q2W or 480 mg Q4W.[51] These doses have comparable time-averaged concentrations over the respective dosing intervals and were shown to have comparable benefit:risk to that of 3 mg/kg Q2W in advanced renal cell carcinoma. The dose of 240 mg Q2W was selected since this matches the same dose and frequency of administration as that in the nivolumab and ipilimumab combination arm. Having the same nivolumab dosing frequency for the monotherapy and combination arm will allow for a more complete assessment of contribution of ipilimumab to efficacy and safety. Additionally, having the same nivolumab dosing frequency will maintain the study blind by avoiding any operational challenges associated different dosing frequencies across treatment arms.

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 must have signed and dated an IRB/IEC approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2) Type of Participant and Target Disease Characteristics

a) Kidney tumor has been completely resected with negative surgical margins obtained. The randomization must occur greater than 4 weeks and less than (or equal to) 12 weeks from the date of nephrectomy. Partial nephrectomy is allowed provided all inclusion criteria are met.

b) Post-nephrectomy tumor shows RCC with a predominantly clear cell histology, including participants with sarcomatoid features.

c) Pathological TNM staging per AJCC staging version 2010 (refer to Appendix 9 for correlations of classifications in cancer staging systems):

- pT2a, G3 or G4, N0M0
- pT2b, G any, N0M0
- pT3 (a, b, c), G any, N0M0
- pT4, G any, N0M0
- pT any, G any, N1M0

Note 1: Excisional biopsy of all regional lymph node(s) which appear abnormal on pre-operative scans or at surgery.

In order to properly stratify participants, it is required that the investigator designate the nodal status as either N0 or N1 according to the following criteria which will be captured in the eCRF:

- N0 requires that a participant have no abnormal regional lymph nodes on pre-operative scans or visualized at surgery, OR have regional lymph nodes biopsied with negative (no tumor present) result.
- N1 requires that a participant have regional lymph nodes biopsied with one or more regional lymph nodes having positive (tumor present) results.

Note 2: Participants with ipsilateral multicentric RCC are eligible if the most advanced lesion per pT stage fulfils the aforementioned combinations of pathologic staging and Fuhrman nuclear grading.

d) Participants must have no clinical or radiological evidence of macroscopic residual disease or distant metastases (M0) after nephrectomy:

- Baseline tumor assessment, performed 4 to approximately 12 weeks after nephrectomy, shows no metastasis or residual tumor lesions per local review and as confirmed by BICR. Results of BICR of the baseline tumor assessment confirming absence of metastasis or residual tumor lesions must be received before randomization.

- If the Investigator is not certain the participant is disease free, the participant should 1) not be consented or be enrolled into the study and 2) evaluation for eligibility should not be submitted to BICR.

Note: participants with one or more regional lymph nodes identified with short axis ≥ 15 mm on the baseline (post-operative) tumor assessments are considered to have gross residual disease and are therefore ineligible. See Section 9.1.2 for guideline of imaging diagnosis for baseline disease-free status.

e) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 (Appendix 5).

f) Either a FFPE tissue block or unstained tumor tissue sections, obtained within 3 months prior to enrollment, preferably from nephrectomy, with an associated pathology report, must be submitted to the central laboratory prior to randomization. FFPE block or 20 unstained slides is ideal, but a minimum of 10 unstained slides will be acceptable if tumor tissue is limited. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is unacceptable for submission. Sites will be notified if there is insufficient tissue for analysis by the central lab.

3) Age and Reproductive Status

a) Males and Females, ages ≥18 years or age of majority.

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.

i) An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

ii) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Assessments.

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

c) Women must not be pregnant or breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception and use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency (Appendix 4 and as described below and included in the ICF) for the duration of treatment with study treatment(s) nivolumab plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

i) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

ii) WOCBP must agree not to donate eggs (ova, oocytes) for the purpose of reproduction during the intervention period and for at least 5 months.

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

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

e) **Not Applicable per Revised Protocol 04:** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) nivolumab plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) **Not Applicable per Revised Protocol 04:** Azoospermic males are exempt from contraceptive requirements. **Still applicable per Revised Protocol 04:** WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug to a developing fetus. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at all sites where mandated by country or local regulations (see Appendix 7).

b) Any severe or serious, acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, including ongoing or active infection requiring parental antibiotics.

c) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Topical, ocular, intra-articular, intranasal, inhaled steroids, and adrenal replacement steroid doses > 10 mg daily prednisone or the equivalent are permitted in the absence of active immune disease.

d) Uncontrolled adrenal insufficiency.

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

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

Note: Participants with a history of RCC who have been considered cured with a nephrectomy or other surgical procedure in the past, and now present with a new RCC, either on the same kidney or the contralateral kidney, should not be enrolled into the study.

g) Treatment with any live / attenuated vaccine within 30 days of first treatment.

i) The use of inactivated vaccines, such as the seasonal influenza (eg, Fluzone®) will be permitted on study without restriction.

h) Previous SARS-CoV-2 infection (either suspected or confirmed) within 4 weeks prior to screening.

Acute symptoms must have resolved and based on investigator assessment in consultation with the medical monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

2) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Prior systemic anti-cancer treatment, including chemotherapy, antiangiogenic agents or investigational agents, given in the neoadjuvant, adjuvant, or metastatic setting for RCC.

c) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

d) Participants currently in other interventional trials, including those for Coronavirus Disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol specific washout period is achieved. 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, as determined by discussion between the investigator and the BMS Medical Monitor.

3) Physical and Laboratory Test Findings

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

b) WBC < 2000/µL

c) Neutrophils < 1500/µL

d) Platelets < 100 x 10^3/µL

e) Hemoglobin < 9.0 g/dL

f) Serum creatinine >1.5 x ULN unless creatinine clearance ≥ 40 mL/min (measured or using the Cockcroft-Gault formula)

g) AST/ALT > 3.0 x ULN

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

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity to a monoclonal antibody.

b) History of allergy or hypersensitivity to study drug components.

5) Other Exclusion Criteria

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

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

Retesting of laboratory parameters and/or other assessments within the 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.

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 considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Symptoms (eg, cough, shortness of breath) have resolved, and

- In the opinion of the Investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up test for SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines

7 TREATMENT

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

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

An 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.

In this protocol (see Table 7-1), the following are considered IP/IMP:

- Nivolumab (BMS-936558)
- Ipilimumab (BMS-734016)
- Nivolumab-Placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection)
- Ipilimumab-Placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection)

The 0.9% normal saline or 5% dextrose to be used as placebo will not be provided by the Sponsor.

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 CA209914					
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IMP**	**Blinded or Open Label[a]**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab Solution[b] for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	IP	Open-label	5 or 10 vials per carton Or 240 mg kits (two 100 mg vials and one 40 mg vial) Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8 °C. Protect from light and freezing
Ipilimumab	200 mg (5 mg/mL)	IP	Open-label	4 vials per carton Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8 °C. Protect from light and freezing
0.9% Sodium Chloride for Injection	NA	IP	Open-label	Various (local commercial product)	As per active IP
5% Dextrose for Injection	NA	IP	Open-Label	Various (local commercial product)	As per active IP

[a] The term "open-label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion.

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

Premedications used to treat infusion reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent or placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative sites if available and permitted by local regulations

7.1 Treatments Administered

7.1.1 Administration

Participants should receive nivolumab at a dose of 240 mg as an approximately 30-minute infusion on Day 1 of each treatment cycle until recurrence, unacceptable toxicity, withdrawal of consent, Week 36, or a maximum of 12 doses, whichever occurs first. Starting with Cycle 1, ipilimumab 1 mg/kg as an approximately 30-minute infusion should be administered every third cycle (ie, Cycles 1, 4, 7, and 10). Table 7.1.1-2 provides the dosing schedule. Participants must begin study treatment within 3 calendar days of randomization.

Treatment cycles should be given every 2 weeks (14 days). After Cycle 1, dosing for subsequent dosing should be based on the actual date of administration of the previous cycle. To permit scheduling flexibility (eg, to accommodate local holidays), doses may be given up to 2 days early (ie, no less than 12 days after the previous cycle) or up to 17 days after the previous cycle. Doses given more than 17 days after the previous dose will be considered delayed.

For Cycles 1, 4, 7, and 10, when 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 0.9% normal saline or 5% dextrose flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred. Simultaneous infusions of nivolumab and ipilimumab will not be permitted.

Ipilimumab dosing calculations should be based on the body weight assessed at either the day of dosing 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 ipilimumab doses should be rounded to the nearest milligram.

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Premedications are not recommended for nivolumab or ipilimumab on the first cycle. Participants should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.3.

Doses of nivolumab and ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not to be skipped/omitted, only delayed if any dose delay criteria are met. Dose delay criteria and criteria to resume treatment are discussed in Section 7.4.

Any cycles not given within 36 weeks after the first dose will be omitted. Participants who have not completed all 12 cycles will discontinue study treatment at Week 36 and begin the Post-Treatment Follow-Up Phase.

The strength and route of administration are described in Table 7.1.1-1 and the timing of each dose is described in Table 7.1.1-2.

Table 7.1.1-1: Strength and Route of Study Treatment Administration

Study Treatment	Unit dose strength(s)/Dosage level(s)	Route of Administration
Nivolumab	240 mg	IV
Ipilimumab	1 mg/kg	IV
Nivolumab-Placebo	0.9% Sodium Chloride or 5% Dextrose Injection)	IV
Ipilimumab-Placebo	0.9% Sodium Chloride or 5% Dextrose Injection)	IV

Table 7.1.1-2: Dosing Schedule for CA209914

Arm	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 Day 1	Cycle 8 Day 1	Cycle 9 Day 1	Cycle 10 Day 1	Cycle 11 Day 1	Cycle 12 Day 1
Arm A (Parts A and B) Nivolumab + Ipilimumab	N240 + I1	N240	N240	N240 + I1	N240	N240	N240 + I1	N240	N240	N240 + I1	N 240	N 240
Arm B (Parts A and B) Placebo	N Placebo + I Placebo	N Placebo	N Placebo	N Placebo + I Placebo	N Placebo	N Placebo	N Placebo + I Placebo	N Placebo	N Placebo	N Placebo + I Placebo	N Placebo	N Placebo
Arm C (Part B only) Nivolumab + I Placebo	N240 + I Placebo	N240	N240	N240 + I Placebo	N240	N240	N240 + I Placebo	N240	N240	N240 + I Placebo	N240	N240

I1 = ipilimumab 1 mg/kg; I Placebo = ipilimumab placebo; N240 = nivolumab 240 mg; N Placebo = Nivolumab Placebo.

Note: Time between end of nivolumab infusion and start of ipilimumab infusion should allow time for flushing of line, changing of filters, and observation for infusion reaction.

7.1.1.1 Nivolumab

Nivolumab Injection 100 mg/10 mL (10 mg/mL) and Nivolumab Injection 40 mg/4 mL (10 mg/mL) are to be administered as an approximately 30-minute IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection. For instructions on dilution and infusion of nivolumab injection, please refer to the clinical protocol, current IB, pharmacy manual/binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. At the end of the infusion, flush the line with a sufficient quality of 0.9% normal saline or 5% dextrose solution.

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

7.1.1.2 Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC, non-PVC/non-DEHP or glass container and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). For ipilimumab storage instructions and additional preparation instructions, refer to Ipilimumab IB and/or pharmacy manual/reference sheets.

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

Ipilimumab is to be administered as an approximately 30-minute IV infusion after the completion of the nivolumab infusion. A volumetric pump with a 0.2 to 1.2 micron, low protein binding, in-line filter is to be utilized. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injections. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of 0.9% normal saline or 5% dextrose solution.

7.2 Method of Treatment Assignment

CA209914 is a double-blind, randomized trial. Participants with early stage localized RCC who underwent radical or partial nephrectomy will be eligible to participate. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling the IRT to obtain a participant number. Every participant that signs the ICF must be assigned a participant number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. 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
- Date of birth, where applicable by local regulations
- Gender at birth

Once enrolled in IRT participants who have met all eligibility criteria will be ready to be randomized through IRT. The following information is required for participant randomization:

- Participant number
- Date of birth, where applicable per local regulations
- TNM staging per AJCC staging version 2010 and Fuhrman nuclear grading categories (refer to Appendix 9 for correlations of classifications in cancer staging systems):
  - pT2a, G3 or G4, N0, M0
  - pT2b, G any, N0, M0
  - pT3, G any, N0, M0
  - pT4, G any, N0, M0
  - pT any, G any, N1, M0
- Type of nephrectomy procedure (partial versus radical, including total nephrectomy).
- Date of nephrectomy
- Confirmation that tumor tissue has been sent to the central lab.
- Confirmation of disease-free status by BICR (radiographic only)

Refer to Section 6.1 for the definition of node status. The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the BMS Medical Monitor or designee, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the participant has been made.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor or designee.

For this study, the method of unblinding for emergency purposes is through the IRT. For information on how to unblind for emergency, please consult the IRT manual.

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

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded 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) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.3.1 Unblinding at the Time of Disease Recurrence

If a participant is assessed by the investigator to have RCC disease recurrence (Section 9.1.3.2), the study treatment assignment for the participant can be obtained by the investigator through IRT for non-emergency unblinding in order to determine subsequent anti-cancer treatments. The investigator should follow the procedures outlined in the IRT manual to obtain the participant's study treatment assignment.

Investigators are strongly encouraged to wait for confirmation of recurrence from the BICR prior to non-emergency unblinding for the purpose of initiating subsequent anti-cancer therapy, unless clinical considerations require immediate intervention (eg, symptomatic brain metastases). If a tumor biopsy collection at the time of suspected recurrence is planned, the request for unblinding should occur after pathology results are available. If subsequent anti-cancer therapy (including systemic cancer therapy, radiotherapy, or tumor-directed surgery) is planned prior to BICR confirmation of recurrence, the investigator must contact the BMS Medical Monitor or designee to discuss the case prior to the start of any of such therapy.

If a participant is diagnosed with a non-RCC secondary cancer, blinding should be preserved unless specific circumstances, to be discussed with the BMS Medical Monitor or designee, require that the blind be broken (eg, participant has metastases and could enroll on a clinical trial but would be ineligible if he or she had prior checkpoint inhibitor therapy).

For this study, the method of unblinding for emergency purposes is through the IRT. For information on how to unblind in an emergency, please see Section 7.3.

7.4 Dosage Modification

Dose reductions or dose escalations are not permitted. All dose modifications rules apply to both Arms A and B given the blinded nature of this study.

7.4.1 Dose Delay Criteria for Study Treatment

Regardless of whether or not the event is attributed to Arm A, Arm B, or Arm C, all study drugs must be delayed until criteria to resume treatment (Section 7.4.2) have been met, given the blinded

nature of this study. Tumor assessments for all participants should continue as per protocol even if dosing is delayed. If one drug is delayed, both study drugs must be delayed.

Study drug administration should be delayed for any of the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- SARS-CoV-2 infection (either suspected or confirmed).

Participants who require delay of study drug should be re-evaluated weekly or more frequently if clinically indicated and resume study drug dosing when re-treatment criteria are met. If a participant is delayed beyond 36 weeks of the first dose, treatment will discontinue.

7.4.2 Criteria to Resume Treatment

All criteria to resume study therapy apply to nivolumab, ipilimumab, and placebo, given the blinded nature of the study. Participants may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value and any systemic corticosteroids have been tapered to ≤ 10 mg prednisone equivalent. (See Section 7.7.3 for exception regarding adrenal replacement steroids.)

The following are exceptions to the above:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor or designee.
- Participants with SARS-CoV-2 infection (either suspected or confirmed) may resume treatment after all of the following: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications), 3) evaluation by the Investigator with confirmation that there are

no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

If the criteria to resume treatment are met after a delay of Cycle 4, 7, or 10, then both nivolumab and ipilimumab must be resumed on the same day when the cycle is given.

If treatment is delayed > 6 weeks from the previous dose, the participant must be permanently discontinued from study therapy, except as specified in Section 8.1.1.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor or designee. Grade 3 or 4 drug-related adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

7.4.3 Treatment of Study 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. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Regardless of whether or not the event is attributed to the study drugs, all Grade 3 or 4 infusion reactions should be reported within 24 hours to the study BMS Medical Monitor or designee and reported as an SAE if it meets the criteria, given the blinded nature of the study. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 study drug administrations.

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

- Stop the study 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 drug 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 study drug 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 drugs will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 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 (eg, required diluents, administration sets).

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the CA209914 Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF. This will be source data verified by the BMS Unblinded Site Monitor through regularly scheduled monitoring visits.

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 AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents given prior to discontinuation of study treatment)
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella; zoster; yellow fever; rotavirus; oral polio; and measles, mumps, rubella [MMR]) during treatment, and until 100 days post last dose.
  - Note: The use of inactivated vaccines, such as seasonal influenza (eg, Fluzone), will be permitted on study without restriction.

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

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.

Investigators are strongly encouraged to wait for confirmation of recurrence from the BICR prior to initiating subsequent systemic cancer therapy, radiotherapy, or tumor-directed surgery for suspected recurrence unless clinical considerations require immediate intervention (eg, symptomatic brain metastases). If subsequent systemic cancer therapy, radiotherapy, or tumor-directed surgery is planned prior to BICR confirmation of recurrence, the investigator must contact the BMS Medical Monitor or designee to discuss the case prior to the start of any of these procedures.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses, even if > 10 mg/day prednisone equivalents, 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.

Concomitant medications are recorded at baseline, throughout the treatment phase of the study and within 100 days of the last dose date of study drug should be recorded in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

7.8 Treatment After the End of the Study

At the end of the study/Period (24 weeks), BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by 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
- Criteria listed in Section 8.1.1
- Disease recurrence or occurrence of a secondary malignancy which requires systemic therapy or radiotherapy for treatment

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 notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant

during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor or designee within 24 hours of awareness of the pregnancy. If 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/designee must occur.

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

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

8.1.1 Study Treatment Discontinuation Criteria

- All discontinuation criteria apply to nivolumab, ipilimumab, and placebo given the blinded nature of the study. Treatment should be permanently discontinued for any of the following:
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related adrenal insufficiency requires discontinuation .
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*

        * In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable

benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), requires discontinuation
- Grade 4 drug-related adrenal insufficiency or hypophysitis requires discontinuation
- The following Grade 4 events are exceptions and do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days.
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy AE, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor or designee.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AE 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 or designee.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor or designee must be consulted. Tumor assessments should continue per protocol schedule even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing delays.

Study treatment must be discontinued within 36 weeks after the first dose. Any cycles not given within 36 weeks after first dose will be omitted.

8.1.2 Post Study Treatment Study Follow-up

In this study, DFS is a key endpoint of the study. 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/randomized participants outside of the protocol defined window (see Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all 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 CT/MRI procedures and timing are summarized in the Section 9.1.2.
- 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 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AE, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) IB and in Appendix 6.

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

Study evaluations will take place in accordance with the Schedule of Activities in Section 2.

9.1.1 Definitions of Recurrence

- The primary endpoint of DFS is defined as time from randomization until death from any cause or recurrence of tumor as defined by either of the following:
- Local disease recurrence refers to relapse of the primary tumor in-situ (site of original resected primary RCC tumor, either in the surgical bed of the resected kidney or in the residual kidney in partial nephrectomy) or occurrence of a secondary RCC primary cancer

- Distant recurrence: any non-local metastatic sites
- The date of recurrence is defined as the date of the tumor assessment that demonstrated unequivocal recurrence.

For participants with suspected diagnosis of secondary non-RCC primary tumor, the investigator should clearly document the tumor site(s). These events will not be counted as an event under the primary study endpoint.

9.1.2 Methods of Measurements

CT and MRI are an essential part of the work-up to establish recurrence. Contrast-enhanced CT of the chest, abdomen, and pelvis should be performed. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous).

- 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 MR 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.
- Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.
- PET alone will not be considered adequate for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.

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

- Histology or cytological evidence of recurrence should be attempted in all cases except for brain metastases. Cytology and/or histology are mandatory to confirm recurrence in solitary or in equivocal lesions, any new lesions occurring in the kidney, and lymph nodes unless the lesion is too small to biopsy or the risk of biopsy is substantial (eg, inter-aortal node with risk

of bleed after biopsy because of close proximity to the aorta and IVC) in which case the recurrence must be confirmed with a repeat scan 4 weeks later.

9.1.3 Imaging and Clinical Assessment

9.1.3.1 Assessment of Baseline Disease-free Status

Screening/baseline imaging is to be performed greater than 4 weeks post-nephrectomy and submitted to the radiology vendor for BICR confirmation of disease-free status. Pre-nephrectomy images are also requested, if available.

Participant eligibility must be confirmed by BICR prior to randomization, and randomization must occur within 12 weeks post-nephrectomy.

Therefore, sites are strongly encouraged to submit pre-nephrectomy scans (if available) and baseline scans to BICR preferably prior to 8 weeks after the nephrectomy to allow for return of the results from the BICR.

9.1.3.2 Investigator Assessment of Recurrence

The same method of assessment used at Screening should be used for on-study time points. Post-baseline assessments will be performed at the time points described below until disease recurrence confirmed by BICR, death, or withdrawal from the study.

Timing for scans should be based on the date of first treatment, which is considered Week 1.

Tumor assessments for ongoing study treatment decisions will be completed by the investigator.

1) First tumor assessment post-baseline should be performed at Week 23 (± 1 week). Use same imaging method as was used at screening/baseline.
2) Subsequent tumor assessments should occur at Weeks 36 and 52. Allowable window for assessments is ± 1 week. After Week 52 (first year), tumor assessments should occur every 6 months (± 2 weeks) until Year 6 and then annually (± 2 weeks) for Year 6 to Year 10.
3) Additional imaging of potential disease sites should be performed whenever disease recurrence or occurrence of a secondary malignancy is suspected. Brain CT or MRI with contrast or bone imaging during on-study treatment and follow-up periods should be obtained if clinically indicated.
4) Tumor assessments can be discontinued when recurrence has been confirmed by BICR.

General Considerations for Determining Recurrence:

1) The goal is to identify lesions suspicious for recurrence of RCC. If it is believed that a lesion is NOT malignant in nature (eg, infection, trauma), it should be noted in the medical records. The specified minimum size criteria should be combined with radiographic appearance consistent with recurrent tumor in the assessment of all suspicious lesions.

2) Equivocal recurrence is upgraded to unequivocal recurrence (except in cases of central nervous system [CNS] recurrence) by one or more of the following:
   a) A subsequent scan not earlier than 4 weeks from the time when recurrence was first suspected demonstrates that the lesion size is ≥ 5 mm over the size previously recorded, or the radiographic appearance of the lesion has become consistent with tumor recurrence. If this occurs, the date of recurrence will be the date when the lesion was first suspected.
   b) FDG PET demonstrates qualitative uptake consistent with malignancy.
   c) Positive histology/cytology.
3) Appearance of multiple new lesions in the same time point generally constitutes unequivocal recurrence, even though they may be from different organs (eg, one liver lesion, one lung lesion, and one enlarged lymph node).

The diagnosis by radiographic recurrence of localized RCC or distant metastasis or occurrence of a secondary malignancy can be made only when the imaging findings meet the acceptance criteria in Table 9.1.3.2-1. Positive cytology or histology of a suspected lesion will also confirm recurrence.

Table 9.1.3.2-1: Criteria for Diagnosis of Radiographic Recurrence

Anatomic Sites	Criteria
Kidney	1) Equivocal renal lesions include: d) Equivocal secondary RCC primary tumor (eg, in contralateral kidney): Any renal lesion measuring < 40 mm in LD or with radiographic appearance equivocal for new primary RCC tumor noted by the reader. e) Equivocal recurrent lesions: Any new lesion of any size in the ipsilateral kidney (after partial nephrectomy) or nephrectomy bed (after radical nephrectomy). 2) Unequivocal renal lesions include: a) Unequivocal secondary RCC primary tumor (eg, in contralateral kidney): One or more renal lesions measuring ≥ 40 mm in LD and with radiographic appearance consistent with a new primary or recurrent tumor. 3) Unequivocal recurrent lesions: a) Refer to the second bullet under the previous section, "General Considerations for Determining Recurrence."
Non-Nodal Soft Tissue (including visceral lesions)	2) Equivocal lesions include: b) Solitary lesion measuring ≤ 10 mm in LD or with radiographic appearance equivocal for tumor recurrence. c) One or more lesions suggestive of intraperitoneal seeding/implants or port site recurrence (eg, in subjects who underwent prior laparoscopic or robotic surgery). 4) Unequivocal lesions include: One or more new lesions > 10 mm in LD with radiographic appearance consistent with tumor recurrence (excluding intraperitoneal lesions).
Bone Lesions	3) Equivocal lesions include: a) Solitary lesion.

Table 9.1.3.2-1: Criteria for Diagnosis of Radiographic Recurrence

Anatomic Sites	Criteria
	b) Lesions identified on radionuclide bone scan. Findings on radionuclide bone scan must be confirmed by CT, MRI, or plain films in order to be upgraded to unequivocal. 5) Unequivocal lesions include: Two or more new lesions consistent with tumor recurrence.
Lymph Nodes[a]	4) Normal lymph nodes are defined as < 10 mm in the short-axis diameter (SAD). 6) Equivocal lymph nodes include a) Lymph nodes measuring 10 – 14 mm SAD with radiographic appearance consistent with RCC recurrence. b) Lymph nodes ≥ 15 mm SAD *without* radiographic appearance consistent with RCC recurrence. 7) Unequivocal proof of nodal recurrence includes: One or more previously normal or equivocal lymph nodes that enlarge to ≥ 15 mm SAD and with radiographic appearance consistent with RCC recurrence.
Fluid Collections (eg, ascites, pleural/pericardial effusions)	5) Presence of fluid alone, without pathological confirmation, does not constitute equivocal or unequivocal recurrence. 8) Unequivocal proof of recurrence is positive pathology of malignant cells from fluid(s).
CNS	Unequivocal recurrence is defined as any new CNS lesion of any size on CT or MRI with a radiographic appearance consistent with tumor recurrence.

[a] For lymph node with short axis 10-15 mm, consider biopsy when lymph node is progressively enlarged as evidenced by 2 CT or MRI imagings separated by at least a 4-week interval.

9.1.3.3 BICR Assessment of Recurrence

Sites should submit all scans to a third-party vendor on a rolling basis, preferably within 5 business days of scan acquisition throughout the duration of the study. When recurrence is diagnosed by the investigator per the criteria specified in Table 9.1.3.2-1, the site will inform the radiology vendor by indicating on the submission form that recurrence has been identified, so that the BICR assessment of recurrence can be performed. Any relevant cytology/pathology results that support a diagnosis of recurrence should be promptly submitted to ICON Central Lab so they can be translated and de-identified before being sent to BICR. The BICR review will be completed and the results provided to the same site within 10 business days of receipt of the scans and any relevant cytology/pathological data, provided there are no pending imaging queries to the site.

Participants whose recurrence is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until the BICR confirms recurrence on a subsequent tumor assessment.

If the investigator feels that the immediate initiation of subsequent therapy is clinically indicated and does not wish to wait for the results of the BICR, then the decision to break the blind must be discussed with the BMS Medical Monitor or designee prior to doing so. When the blinding code

is broken, the reason must be fully documented in the site source document. Please see Section 7.3 for additional information regarding unblinding.

9.1.3.4 Date of Recurrence

The first date when recurrence was observed should be taken into account regardless of the method of assessment. Please note the following general rules regarding the assessment of recurrence:

- If recurrence is unequivocal (eg, multiple measurable lesions), confirmation with histology/cytology should be attempted, but not required.
- If recurrence is equivocal (eg, lymph node only, solitary lesion, or in the kidneys), confirmation with histology/cytology must be attempted. If risk of biopsy is too high or biopsy not feasible, either a follow-up CT or MRI scan showing progressive and measurable disease or PET/CT demonstrating unequivocal FDG uptake must confirm recurrence. If confirmed, the date of initial scan showing recurrence will be recorded as the recurrence date.
- Any pathological evidence of malignancy denotes recurrence (even if scans are equivocal or not available).
- If both pathology and imaging are available and meet the criteria for recurrence, specified in Table 9.1.3.2-1, the date of recurrence is the date of which ever examination came first.

9.1.4 Imaging Restriction and Precautions

Table 9.1.4-1 provides a summary of the alternative methods, acceptable per protocol, in the event of contraindications for use of IV and oral contrast, and or/MRI.

Table 9.1.4-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

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

Table 9.1.4-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods
		• MRI without contrast can be used as a second alternative method if a participant has clinical contraindications for both contrast-enhanced CT and MRI
Bone	Bone scintigraphy	PET (18F-fluoride NaF or FDG) and 99m Technetium SPECT

Notes:

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

The use of gadolinium-based contrast agents in participants with acute or chronic renal insufficiency, with a glomerular filtration rate (GFR) less than 30 mL per minute per 1.73 m^2 or with any acute renal failure caused by hepatorenal syndrome or perioperative liver transplantation, is not recommended.

If gadolinium is contraindicated, proceed without contrast, but the reason for not using contrast must be documented.

9.1.5 Outcomes Research Assessments

The evaluation of patient-reported outcomes is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into 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. Patient-reported outcomes will be captured through the use of 2 validated self-reported questionnaires: the NCCN Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) and the EuroQoL Group's 3-level version of the EQ-5D (EQ-5D-3L). The questionnaires will be provided in the participant's preferred language and may be administered by telephone during follow-up visits 1 and 2 and subsequent survival follow-up visits. All patient-reported outcome assessments should be completed prior to study-related procedures, if possible. There exists a standardized guide that can be used to facilitate telephone administration of the EQ-5D-3L, though a similar guide does not exist for the FKSI-19. Participants will be provided with a hard copy of the latter scale to take home and use as a visual aid during telephone interviews.

The NCCN FKSI-19 is a 19-item scale that measures tumor specific HrQoL in kidney cancer participants.[52] The symptom index questionnaire is broken into 4 subscales: disease-related symptoms-physical (DRS-P), disease-related symptoms-emotional (DRS-E), treatment side-effects (TSE), and general function and well-being (FWB). Additionally, a 9-item subset of disease-related symptoms knows as the FKSI-DRS will be examined. The FKSI-19 uses 5 Likert-type response categories that range from “not at all” to “very much.” Participants are asked to circle the response category that best characterizes their response over the last 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea, and ability to work. The FKSI-19 uses a recall period of the past 7 days.

The EQ-5D-3L is a standardized instrument used to measure self-reports of health status and functioning.[53] The instrument’s descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes 35 = 243 health states. Empirically derived weights can be applied to an individual’s responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for Japan, UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from “best imaginable” to “worst imaginable” health. The EQ-5D is available for use in over 150 languages.

Table 2-2 and Table 2-3, provide information regarding the timing of patient-reported outcomes assessments.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

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

Contacts for SAE reporting are specified in Appendix 3.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (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 CRF.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Non-serious AE Collection

The collection of non-serious AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection, which should begin collection at the time of consent) should begin at initiation of study treatment until 100 days after the last dose at the time points specified in the Schedule of Activities (Section 2). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

SAE Collection

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the Screening Phase and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). 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.

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

SARS-CoV-2 Infection-related AE Collection

All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

Extended Collection of Study Treatment-related Non-Serious AEs

The time period for collection for study treatment-related AEs is being extended to better characterize and understand late-onset AEs considered related to study treatment. This will provide important safety data in the adjuvant setting and better understand the safety profile. The collection of non-serious AEs considered related to the study treatment should continue to be collected through Survival Follow-up visits until approximately 1 year following discontinuation of study treatment.

However, if the non-serious AE has an onset date after 100 days since the last dose of study treatment and it occurs on or after the initiation of subsequent anti-cancer therapy, it should not be reported.

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

All non-serious AEs (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.

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.1) and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled out.

After Follow-up visit 2 and through the survival follow-up phase, all study treatment-related AEs (non-serious and SAEs) should be collected during the survival follow-up visits. However, if the non-serious AE has an onset date after 100 days since the last dose of study treatment and it occurs on or after the initiation of subsequent anti-cancer therapy, it should not be reported. After the initial AE/SAE report, the investigator is required to proactively follow each participant at

subsequent visits/contacts. All AEs (SAEs and non-serious) considered related to study treatment will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A 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.

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

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.

Note: The following paragraph is no longer applicable per Administrative Letter 10. 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 non-serious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.2.9 Management Algorithms

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology

agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

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

The above algorithms are found in the Nivolumab IB and in Appendix 6.

9.3 Overdose

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. See the Schedule of Activities for specific assessments and time points.

9.4.2 Imaging Safety Assessment

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

9.5 Pharmacokinetics

Samples for PK and immunogenicity assessments will be collected for all participants as described in Table 9.5-1. All time points are relative to the start of study drug administration. Placebo samples will not be analyzed. All on-treatment time points are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted,

the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored according to the Laboratory Manual.

Serum concentration analyses for nivolumab and/or ipilimumab will be performed by validated immunoassay bioanalytical method(s) for nivolumab and ipilimumab.

Samples collected from participants will be evaluated for the development of Anti-Drug Antibody (ADA) for nivolumab and/or ipilimumab by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab.

In addition, selected serum samples may be analyzed by an exploratory method that measures nivolumab and ipilimumab, or detect anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, immunogenicity or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on suspected immunogenicity related AE).

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab, Ipilimumab and Placebo for all Study Parts and Arms

Study Day[a] (1 Cycle = 2 weeks)	Event (Relative to Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab/Placebo	Immunogenicity Blood Sample for Nivolumab/Placebo	Pharmacokinetic Blood Sample for Ipilimumab/Placebo	Immunogenicity Blood Sample for Ipilimumab/Placebo
C1D1	Predose[b]	00:00	X	X	X	X
C1D1	(EOI-PK)[c]	00:30	X		X	
C2D1	Predose[b]	00:00	X	X	X	X
C5D1	Predose[b]	00:00	X	X	X	X
C8D1	Predose[b]	00:00	X	X	X	X
C11D1	Predose[b]	00:00	X	X	X	X
Follow-up Samples (Follow-up 1 and Follow-up 2)- 30 and 100 days, respectively, from the last dose of study therapy (see Table 2-3 for additional details)	NA	NA	X	X	X	X

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

[b] Predose: All predose samples for nivolumab (or placebo) and ipilimumab (or placebo) should be taken prior to the start of nivolumab (or placebo) infusion. It is acceptable to obtain predose samples with routine lab work if done on the same day as the infusion, provided accurate collection time is indicated for the sample.

If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

c EOI-nivo and EOI-ipi: End of Infusion samples for nivolumab and ipilimumab, respectively**.** EOI-PK collection instructions apply to the placebo arm as well.

. Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK for both nivolumab and ipilimumab when all of the ipilimumab study drug (which is administered after nivolumab) has been infused. If the site infuses drug without a flush, then collect the EOI-PK samples within approximately 5 minutes after end of infusion of ipilimumab. If a subsequent flush is administered to clear the IV lines of ipilimumab and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush.

Do not draw EOI samples from the same IV access that the drug was administered.

9.6 Pharmacodynamics

Refer to Section 9.8.

9.7 Pharmacogenomics

Refer to Section 9.8.

9.8 Biomarkers

A variety of factors that could potentially predict clinical response and incidence of AEs to nivolumab + ipilumimab combined therapy and/or nivolumab monotherapy will be investigated in peripheral blood and in tumor specimens taken from all participants prior to treatment and as outlined in the protocol. Data from these investigations will be evaluated for associations with efficacy endpoints. In addition, these analyses will provide the necessary data to identify and validate biomarkers with predictive versus prognostic value. The biomarker-sampling schedule for this study is provided in Table 9.8-1. A separate manual outlining details of biomarker sample collection and handling will be provided to participating sites.

Table 9.8-1: Biomarker Sampling Schedule for Nivolumab, Ipilimumab, and Placebo for All Study Parts and Arms

Study Day (1 Cycle = 2 Weeks)	Event (Relative to Dosing) Hour	[a]Tumor Biopsy	Whole Blood DNA	Peripheral Blood RNA[b]	MDSC	Serum[b]	ctDNA[c]	Anti-SARS-CoV-2 serology[d]
Screening		X						
C1D1	Predose		X	X	X	X	X	X
C2D1	Predose						X	
C4D1	Predose					X		
C5D1	Predose						X	
C7D1	Predose				X	X		
C9D1	Predose						X	
C12D1	Predose							X
Follow-up Visit 2								X

AE, adverse event; ctDNA, circulating tumor DNA; C, cycle; D, day; MDSC, myeloid-derived suppressor cells; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

[a] Baseline tumor samples are mandatory and an optional tumor sample will be collected upon recurrence.

[b] Sample collection upon > Grade 3 non-laboratory drug-related AE and/or laboratory abnormalities regarded as a drug-related SAE, to be collected when clinically safe and feasible.

[c] Subsequent ctDNA sample collections will be aligned with tumor assessments performed on Weeks 23, 36, and 52 (+/- 1 week window). If a tumor assessment is not performed, ctDNA sampling is not required.

[d] A sample is also collected approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or immunoglobulin G (IgG)

9.8.1 Additional Research Collection

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

For All US sites:

Additional research is mandatory for all investigational sites in the US.

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 [redacted] 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 DNA from whole blood, serum, circulating tumor DNA (ctDNA), peripheral blood RNA, and DNA and RNA from tumor biopsy tissue, (see Table 9.8.1-1) 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 subject to the recipient's agreement to establish similar storage procedures.

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

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

A variety of factors that could potentially predict clinical response and incidence of AEs to nivolumab and ipilimumab will be investigated in peripheral blood and in tumor specimens taken

from all participants prior to randomization. Data from these investigations will be evaluated for associations with DFS, OS, and distant metastasis-free survival and/or safety (adverse event) data. In addition, analyses of markers between the 2 treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements and/or institutional policies) to assess biomarkers associated with RCC or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

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

Sample Type	Timepoints for which residual samples will be retained
Whole blood (DNA)	All
Serum	All
ctDNA	All
Peripheral Blood RNA	All
Tumor Biopsy (DNA and RNA)	Screening and recurrence

9.8.2 Tissue Specimens

Sufficient tumor tissue specimens collected within 3 months prior to enrollment, preferably at the time of nephrectomy, will be required in the form of a FFPE tissue block or 20 unstained slides. A minimum of 10 slides will be acceptable if tumor tissue is limited. In these situations, it is recommended to consult with the protocol team to discuss the specifics of the case.

The tumor sample may be used to assess putative predictive biomarkers of nivolumab and ipilimumab efficacy and/or to better characterize the tumor-immune microenvironment. Various molecular markers with potential predictive value for the treatment of RCC with nivolumab, ipilimumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-L1, PD-1, PD-L2, TILs or subpopulations of TILs, a Th1 immune mRNA expression signature. In addition, tumor samples will also be used for assessment of tumor recurrence score based on gene signature analysis.[54] These tumor samples may also be used to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab and ipilimumab, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3), and intratumoral immune cell subsets, including macrophages, natural killer (NK) cells and B cells.

In addition, it is recommended, although optional, for tumor tissue samples to be collected upon recurrence. These samples may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T-cell checkpoint receptors and

ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T-regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab and ipilimumab on the expression of potentially relevant predictive and/or prognostic RCC biomarkers. Both the nephrectomy tumor sample and the sample collected upon recurrence may be retrospectively assessed for the expression of other immune-related genes, RNAs and/or proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH).

9.8.3 Exploratory Serum Biomarkers

Blood samples for exploratory serum biomarker analyses will be drawn at the time points specified in Table 2-2 and Table 2-3. Additionally, serum samples will be collected when clinically safe and feasible, upon occurrence of a ≥ Grade 3 drug-related AE and/or any lab abnormality regarded as a drug-related SAE, and upon recurrence. Blood samples will be collected and processed for serum and then put in frozen storage. Serum samples may be assessed by ELISA, seromics, microRNA profiling, ctDNA measurements, metabolomics and/or other relevant multiplex-based protein assay methods for immune or RCC-related factors that will predict for nivolumab or ipilimumab benefit or correlate with nivolumab or ipilimumab-related AEs. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict or correlate with safety or efficacy to nivolumab, ipilimumab or other immunotherapies, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (eg, soluble MICA), ctDNA, and microRNAs (such as, but not limited to, miR-513 and miR19b).

9.8.4 Peripheral Blood RNA

Gene expression analyses of RNA derived from whole blood may provide information on the broad effects of nivolumab and ipilimumab on immune modulation. Thus, genomic expression patterns of whole blood collected at the time points in specified in Table 2-2 and Table 2-3 may be assessed by Affymetrix microarray profiling, qRT-PCR or other gene expression profiling technology, with a particular emphasis on genes with relevant immune function.

9.8.5 Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) are an immune cell population capable of suppressing T cell activation and proliferation. MDSCs will be measured at baseline and on-treatment as described in Table 9.8-1 to assess pharmacodynamic changes or associations with outcome.

9.8.6 Peripheral Blood DNA Mutation Research

The presence of cell-free DNA in circulating peripheral blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from proliferating cells or from cells undergoing apoptosis or other forms of cell death. In patients with cancer, a fraction of this DNA is tumor-derived and is termed ctDNA. Small fragments of DNA, averaging between 180 to 200 base-pairs and representing segments of specific genes, can be amplified with PCR and then sequenced. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations

from the parent tumor, using tissue and plasma from participants with known driver mutations in melanoma or head and neck cancer. Beaming technology may be utilized to count the frequency of mutations in the circulation. Correlation analyses with tumor will be warranted where the data are available. ctDNA will be investigated as a prognostic and predictive biomarker and will be used to monitor changes in tumor mutations during treatment.

9.8.7 Whole Blood for Genotyping

Whole blood samples for exploratory pharmacogenetic assessment will be collected from all participants. Genomic DNA will be extracted and subsequently assessed for SNPs and other genetic variations in candidate genes that may predispose participants to nivolumab or ipilimumab benefit or AEs (unless restricted by local requirements.) Such genes include, but are not limited to, PD-1, PD-L1, PD-L2 and CTLA-4. Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically relevant biomarkers identified by other methodologies described in this section. This sample may be assessed for whole exome sequencing (WES) and rearrangements in the TCR in T cells within the peripheral blood. WES is an efficient way to identify genetic variants that alter protein sequences. An assessment of somatic TCR rearrangements by PCR, sequencing or NextGen sequencing approach will provide information regarding the clonality of a T cell repertoire, which may change with nivolumab and/or ipilimumab treatment. In addition, baseline T cell repertoire may be predictive of nivolumab and/or ipilimumab benefit.

9.8.8 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected. Samples collected from participants receiving nivolumab and/or ipilimumab will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassays.

Samples may also be analyzed for neutralizing antibodies and PK samples (please refer to Table 9.5-1 for immunogenicity sampling schedule) may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs.

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

9.8.9 Other Assessments

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

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 modification to the study design outlined in revprot03 adds a monotherapy arm (nivolumab) and roughly doubles the total sample size with the first approximately 800 randomized 1:1 participants (Part A) to nivolumab + ipilimumab and placebo and the approximately 800 randomized 1:1:2 participants (Part B) to nivolumab + ipilimumab, placebo and nivolumab. Part A participants will be mutually exclusive from Part B participants. The combination analysis in Part A is preserved comparing the nivolumab + ipilimumab arm to the placebo arm in the first approximately 800 nivolumab + ipilimumab and placebo randomized 1:1 participants. Part B is added for the purposes 1) to compare monotherapy nivolumab to placebo and 2) to estimate the contribution of components for the combination of nivolumab + ipilimumab and monotherapy nivolumab.

This section is organized as follows. First, sample size calculations for Part A are presented. Second, the sample size calculations for Part B are presented. The Part B monotherapy comparison is between the nivolumab (approximately 400 participants) and placebo (approximately 200 participants) arms. The additional approximately 200 participants randomized to the nivolumab + ipilimumab arm in Part B will be included in the combination OS analysis hierarchically if the DFS monotherapy test is successful (for more details, see Section 10.3.4). In addition, these nivolumab + ipilimumab Part B participants will be compared to the nivolumab participants to assess the contribution of components (CoC), i.e. to directly estimate the hazard ratio and variance for the contemporaneously randomized nivolumab + ipilimumab versus nivolumab arms.

10.1.1 Part A: Combination Comparison of DFS

The combination comparison sample size is driven by the comparison of DFS between participants randomized to receive nivolumab + ipilimumab versus placebo. Approximately 800 participants will be randomized to the nivolumab + ipilimumab and placebo treatment arms in a 1:1 ratio with DFS medians of 111 and 72 months, respectively, rendering a 62-month study. Note the invocation of revprot03 will initiate the 1:1:2 (i.e. nivolumab + ipilimumab, placebo, nivolumab) randomization (see next section on Monotherapy Comparison of DFS).

Approximately 232 events among the approximately 800 contemporaneously randomized 1:1 participants are expected, ensuring 90% power to detect an average hazard ratio of 0.65 with an overall type I error of 0.05 (two-sided). The number of events and power were calculated assuming an exponential distribution and a delayed treatment effect of 3 months. This design yields a minimal HR of 0.764 (P<0.041) when adjusting for interim analyses using Lan-DeMets alpha spending function.

Given accrual rates of 22 participants per month on average for the entire enrollment period, it is estimated that accrual of 800 participants (ie, 400 participants in each arm) will take approximately 36 months; it will take an additional approximately 26 months to observe the required number of events for the final DFS analysis.

There is 1 planned interim analysis of DFS. Stopping boundaries at the interim analyses will be derived based on the exact number of events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. The DFS interim analysis is expected to occur at approximately 56 months when approximately 204 events are expected to have occurred. This will provide 83% power to detect an overall interim DFS HR of 0.743 (P<0.034) at the pre-specified alpha level using the Lan-DeMets alpha spending function.

In the event that Part B enrollment is still ongoing at the time of observing the required number of events for the interim analysis and target number of events needed for the final analysis is projected in a shorter time interval (approximately within 4 months), then the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted after observing approximately 227 DFS events (required number of events since there is no alpha spending for DFS interim analysis) among all randomized participants. The 227 events are expected to provide 90% power to detect a DFS HR of 0.65 at alpha 0.05 (two-sided).

Table 10.1.1-1 summarizes sample size design parameters and schedule of primary endpoint analysis accounting for an interim and final analyses.

Table 10.1.1-1: Part A Summary of Sample Size Parameters and Schedule of Combination Analyses (with an Interim Analysis)

Primary Endpoint	DFS
Primary analysis population	All Randomized Participants
Accrual rate per month	22
Power	90%
Alpha	0.05 2-sided (0.034 at interim analysis, 0.041 at FA)
Hypothesized Median Control vs Experimental (Months)	72 vs 111
Hypothesized Hazard Ratio	0.65
Critical HR (HR at which a statistically significant difference would be observed) / Difference in median corresponding to a minimally significant effect size (Months)	0.764 / 22
Critical HR at interim analysis / Effect size (Months)	0.743 / 25
Expected events for interim analysis (percentage of target events)	204 (88%)
Timing of interim analysis from FPFV (Months)	56
Accrual Duration (Months)	36
Timing of final analysis (FA) from FPFV (Months)	62
Sample size[a]	800
Target number of events (Event Goal)	232

[a] East version 5.4 was used for sample size / power computation

Table 10.1.1-2 summarizes sample size design parameters and schedule of primary endpoint analysis with one final analysis alone.

Table 10.1.1-2: Part A Summary of Sample Size Parameters and Schedule of Combination Analysis (without an Interim Analysis)

Primary Endpoint	DFS
Primary analysis population	All Randomized Participants
Accrual rate per month	22
Power	90%
Alpha	0.05
Hypothesized Median Control vs Experimental (Months)	72 vs 111
Hypothesized Hazard Ratio	0.65
Critical HR (HR at which a statistically significant difference would be observed) / Difference in median corresponding to a minimally significant effect size (Months)	0.771 / 21.4
Accrual Duration (Months)	36
Timing of final analysis (FA) from FPFV (Months)	61
Sample size[a]	800
Target number of events (Event Goal)	227

[a] East version 5.4 was used for sample size / power computation

10.1.2 Part B: Monotherapy Comparison of DFS

The monotherapy comparison sample size is driven by the comparison of DFS between participants randomized to receive nivolumab versus placebo. Approximately 600 participants will be randomized to the nivolumab and placebo treatment arms in a 2:1 ratio (i.e. as part of the 1:1:2 ratio to nivolumab + ipilimumab, placebo, nivolumab) with DFS medians of 106 and 72 months, respectively, for a total accrual of approximately 56 months (20 additional months from the end of the combo test accrual).

Approximately 91 additional events are expected in the nivolumab arm for a total of 153 events among the 600 participants, ensuring 60% power to detect an average hazard ratio of 0.68 with an overall type I error of 0.05 (two-sided). Note that since the Part B participants are mutually exclusive from Part A participants no hierarchical testing for the primary endpoint is necessary (for more details, see Section 10.3.4). The number of events and power were calculated assuming an exponential distribution and a delayed treatment effect of 3 months. This design yields a minimal HR of 0.71 (P<0.043) when adjusting for interim analyses using Lan-DeMets alpha spending function.

Given accrual rates of 40 participants per month on average for the entire monotherapy enrollment period (1:1:2, thus 30 per month for only the monotherapy and placebo arms), it is estimated that

accrual of 600 participants (i.e., 400 participants to the nivolumab arm and 200 to the placebo arm) will take approximately 20 months; it will take an additional approximately 28 months (84 months from study initiation) to observe the required number of events for the final monotherapy DFS analysis.

There is 1 planned interim monotherapy analysis of DFS. Stopping boundaries at the interim monotherapy analysis will be derived based on the exact number of events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. The DFS interim monotherapy analysis is expected to occur at approximately 76 months when approximately 122 events in the monotherapy and contemporaneous placebo arms are expected to have occurred. This will provide 40% power to detect an overall interim DFS HR of 0.65 ($p<0.025$) at the pre-specified alpha level using the Lan-DeMets alpha spending function.

In the event that the target number of events for the interim analysis and final analysis are projected in a shorter time interval (approximately within 6 months), then the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted after observing approximately 149 DFS events among the randomized participants in the nivolumab and placebo arms (required number of events since there is no alpha spending for DFS interim analysis). The 149 events are expected to provide 60% power to detect a DFS HR of 0.68 at alpha 0.05 (two-sided).

Table 10.1.2-1 summarizes sample size design parameters and schedule of primary endpoint analyses planned in this study.

Table 10.1.2-1: Part B Summary of Sample Size Parameters and Schedule of Monotherapy Analyses (with an Interim Analysis)

Primary Endpoint	DFS
Primary analysis population	All Randomized Participants in Nivolumab and Placebo Arms
Accrual rate per month	40 (or 30 2:1 to N and P)
Power	60%
Alpha	0.05 2-sided (0.025 at mono interim analysis and 0.043 at mono final analysis)
Hypothesized Median Control vs Experimental (Months)	72 vs 106
Hypothesized Hazard Ratio	0.68
Critical HR (HR at which a statistically significant difference would be observed) / Difference in median corresponding to a minimally significant effect size (Months)	0.71 / 29
Critical HR at mono interim analysis / Effect size (Months)	0.65 / 39
Expected events for mono interim analysis (percentage of target events)	122 (80%)
Timing of mono interim analysis from FPFV (Months)	76

Table 10.1.2-1: Part B Summary of Sample Size Parameters and Schedule of Monotherapy Analyses (with an Interim Analysis)

Primary Endpoint	DFS
Accrual Duration (Months)	20
Timing of final analysis (FA for mono) from FPFV (Months)	84
Sample size[a]	600
Target number of events (Event Goal)	153

[a] East version 5.4 was used for sample size / power computation

Table 10.1.2-2 summarizes sample size design parameters and schedule of primary endpoint analysis with one final analysis alone.

Table 10.1.2-2: Part B Summary of Sample Size Parameters and Schedule of Monotherapy Analyses (without an Interim Analysis)

Primary Endpoint	DFS
Primary analysis population	All Randomized Participants in Nivolumab and Placebo Arms
Accrual rate per month	40 (or 30 2:1 to N and P)
Power	60%
Alpha	0.05 2-sided
Hypothesized Median Control vs Experimental (Months)	72 vs 106
Hypothesized Hazard Ratio	0.68
Critical HR (HR at which a statistically significant difference would be observed) / Difference in median corresponding to a minimally significant effect size (Months)	0.71 / 29
Accrual Duration (Months)	20
Timing of final analysis (FA for mono) from FPFV (Months)	84
Sample size[a]	600
Target number of events (Event Goal)	149

[a] East version 5.4 was used for sample size / power computation

10.1.3 Contribution of Components Analysis of DFS:

The contribution of components (CoC) will be assessed. The manner in which CoC will be measured is based on the hazard ratio and variance estimates computed for the contemporaneously randomized (approximately 200 vs 400) nivolumab + ipilimumab arm versus the nivolumab arm.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All enrolled participants	• All participants who signed an informed consent form and were registered into the IRT.
All enrolled Part A participants	• All Part A participants who signed an informed consent form and were registered into the IRT.
All enrolled Part B participants	• All Part B participants who signed an informed consent form and were registered into the IRT.
All treated participants	• All participants who received at least 1 dose of study drug.
All treated Part A participants	• All Part A participants who received at least 1 dose of study drug. This is the primary dataset for the Part A drug exposure and safety analysis.
All treated Part B participants	• All Part B participants who received at least 1 dose of study drug. This is the primary dataset for the Part B drug exposure and safety analysis.
All randomized participants	• All participants who were randomized to any treatment arm in the study. This population is considered the population for the combination overall survival analysis contingent on the primary DFS monotherapy analysis (for more details, see Section 10.3.4).
All randomized Part A participants	• All Part A participants who were randomized to any treatment arm in the study. This population is considered for Part A as the primary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics, efficacy analysis and outcome research analysis will be performed in this population.
All randomized Part B participants	• All Part B participants who were randomized to any treatment arm in the study. This population is considered for Part B as the primary efficacy analysis population. Analysis of demography, protocol deviations, baseline characteristics, efficacy analysis and outcome research analysis will be performed in this population.
PK participants	• All randomized participants with available serum time-concentration data.
PK Part A participants	• All Part A randomized participants with available serum time-concentration data.
PK Part B participants	• All Part B randomized participants with available serum time-concentration data.
Immunogenicity Evaluable Participants	• Nivolumab ADA Evaluable Participants: all treated participants with baseline and at least 1 post-baseline pre-infusion nivolumab immunogenicity assessment. • Ipilimumab ADA Evaluable Participants: all treated participants with baseline and at least 1 post-baseline pre-infusion ipilimumab immunogenicity assessment.

Population	Description
Immunogenicity Part A Evaluable Participants	• Nivolumab ADA Part A Evaluable Participants: all Part A treated participants with baseline and at least 1 post-baseline pre-infusion nivolumab immunogenicity assessment. • Ipilimumab ADA Part A Evaluable Participants: all Part A treated participants with baseline and at least 1 post-baseline pre-infusion ipilimumab immunogenicity assessment.
Immunogenicity Part B Evaluable Participants	• Nivolumab ADA Part B Evaluable Participants: all Part B treated participants with baseline and at least 1 post-baseline pre-infusion nivolumab immunogenicity assessment. • Ipilimumab ADA Part B Evaluable Participants: all Part B treated participants with baseline and at least 1 post-baseline pre-infusion ipilimumab immunogenicity assessment.
Biomarker participants:	All randomized participants with available biomarker data (PD-L1 expression status and other assays).
Biomarker Part A participants:	All Part A randomized participants with available biomarker data (PD-L1 expression status and other assays).
Biomarker Part B participants:	All Part B randomized participants with available biomarker data (PD-L1 expression status and other assays).

All analyses will be performed using the treatment arm as randomized (intent to treat), with the exception of dosing and safety, for which the treatment arm as received will be used:

- All randomized participants who take at least 1 dose of double-blind study treatment.
- Participants will be included in the treatment group they were randomized to, eg, data in this data set will be analyzed based on randomized treatment, except in the following cases:
  - If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received.
  - If a participant received study drug from more than 1 treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment received.

10.3 Statistical Analyses

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary DFS analyses will be conducted using a 2-sided log-rank test stratified by pathological T Stage and N Stage status and type of nephrectomy at screening in randomized participants. The hazard ratio and corresponding 2-sided (1- α)% CI (adjusted for interim) will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. DFS curves, DFS medians with 95% CIs, and DFS rates at 6, 12, 18, 24, and 60 months with 95% CIs will be estimated using Kaplan-Meier methodology. Note that upon completion of study enrollment, 2 of the 6 strata levels have less than 20 participants. To avoid unreliable estimates, the strata levels with partial and radical nephrectomy will be combined for stratified analysis purposes. In other words, stratified analysis will be conducted based only on 1 stratification factor (pathological T Stage and N Stage status). For censoring rules, please refer to Table 10.3.1-1.
Secondary	The secondary OS analysis will be conducted using a 2-sided log-rank test stratified by pathology status and histology at screening in randomized participants. The hazard ratio and corresponding 2-sided (1- α)% CI (adjusted for interim) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs and OS rates at 12, 24, 36, 48, and 60 months with 95% CIs will be estimated using Kaplan Meier methodology. Note that upon completion of study enrollment, 2 of the 6 strata levels have less than 20 participants. To avoid unreliable estimates, the strata levels with partial and radical nephrectomy will be combined for stratified analysis purposes. In other words, stratified analysis will be conducted based only on 1 stratification factor (pathological T Stage and N Stage status).
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

Censoring rules for the primary definition of DFS are presented in Table 10.3.1-1. Sensitivity analyses of DFS will be described in the statistical analysis plan.

Table 10.3.1-1: Censoring Scheme Used in Primary Definition of DFS

Situation	Date of Progression or Censoring	Outcome
Recurrence	Date of first recurrence	Event
Death from any cause without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored

Table 10.3.1-1: Censoring Scheme Used in Primary Definition of DFS

Situation	Date of Progression or Censoring	Outcome
New systemic anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-RCC primary cancer reported without recurrence reported prior to or on the same day	Date of last evaluable disease assessment prior to or on the same date of diagnosis of secondary non-RCC primary cancer	Censored

10.3.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary	Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs up to 30 and 100 days of last dose of study therapy will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.
Exploratory	Will be described in the statistical analysis plan, which will be finalized before database lock.

10.3.3 Other Analyses

10.3.3.1 Pharmacokinetic Analyses

The nivolumab and ipilimumab concentration versus time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic (if applicable) covariates on the PK of nivolumab and ipilimumab to determine measures of individual exposure (such as peak, trough and time-averaged concentration following a single dose or at steady state). Pharmacokinetic drug-drug interaction between nivolumab and ipilimumab will be studied by population PK approach as appropriate. Model determined exposures may be used for exposure -response analyses of selected efficacy and safety endpoints, if appropriate. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately, as needed.

10.3.3.2 Biomarker Analyses

Methodology for exploratory biomarker analyses will be described in the statistical analysis plan.

10.3.3.3 Outcomes Research Analyses

Descriptive summary statistics of quality of life assessments will be presented at baseline and each on-study time points unless otherwise specified. Mean changes from baseline for each of the 2 assessments and all associated subscores will be calculated for each treatment arm at each on-

study time point. More specifically, summary scores of the FKSI-19 subscale and total scores, the 9-item FKSI-DRS score, and the EQ-5D-3L utility index and VAS at baseline and on-study time points and the 95% CIs will be conducted. For the EQ-5D-3L utility index, the UK preference weightings will be analyzed.[55] In addition, participant compliance will be described per time point by the proportion of participants who filled out the QoL assessments over the numbers of participants known to be alive and eligible for assessment at these time points.

Additionally, t-tests will be conducted to evaluate the differences between nivolumab combined with ipilimumab versus placebo infusions treatment arms as well as the nivolumab versus placebo infusions treatment arms at each time point, and 95% CIs will also be presented.

10.3.4 Interim Analyses and Hierarchical Testing

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

Part A Combination Analyses Timing

One formal DFS interim combination analysis will be conducted at the time when approximately 88% (204) of the total DFS events in the combination and placebo arms have occurred and the time when the total enrollment of both Part A and Part B is expected to be complete. This formal comparison of DFS will allow for early stopping for superiority. The stopping boundaries at the interim and final analyses will be derived based on the exact number of DFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Note that if Part B enrollment is still ongoing at the time of observing the required number of events for the interim analysis and target number of events needed for the final analysis is projected to occur in a shorter time interval (approximately within 4 months), then the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted after the completion of enrollment in Part A and Part B (statistical significance of only one final analysis of DFS is 0.05 [two-sided]).

If the DFS combination analysis is significant, the OS combination analysis will be tested hierarchically. Formal OS interim combination analyses will be conducted at the time when the interim or final DFS combination analysis is significant. This formal comparison of OS will allow for early stopping for superiority.

The OS combination analyses occurring at the time when the DFS combination analysis is significant either after the Part A (approximately 800) participants randomized to the nivolumab + ipilimumab and placebo arms have a minimum of 20 or 26 months of follow-up, which are expected to occur at approximately 56 (62% of the total events) and 62 (70% of the total events) months from study initiation, respectively. These are at equivalent times when the DFS combination analyses of Part A are expected to occur. However, in the situation when the DFS combination analysis is significant at 56 months but OS is not significant at that time, the 62 month DFS analysis will not be necessary and so the second OS combination interim analysis will occur at 70 months (82% of the total events) rather than 62 months (70% of the total events). At the 56- and 62-month (or 70-month) OS combination analyses, approximately 178 and 201 (or 235) events are expected providing 41% and 53% (or 68%) power to detect overall interim OS HRs of 0.68 (P

< 0.009) and 0.70 (P < 0.012) (or 0.74, P < 0.023), respectively, at the pre-specified alpha level using the Lan DeMets alpha spending function.

The final OS combination analysis will take place after the Part A (approximately 800) participants randomized to the nivolumab + ipilimumab and placebo arms have a minimum of 48 months of follow-up, which is expected to occur approximately 84 months from the start of the study. At the time of the final OS combination analysis, approximately 287 events are expected ensuring 85% overall power to detect a final OS hazard ratio of 0.79 (P<0.045).

Part B Monotherapy Analyses Timing

Similarly, 1 formal DFS interim monotherapy analysis will be conducted at the time when approximately 80% (122) of the total DFS events in the monotherapy and contemporaneous placebo arms have occurred. This formal comparison of DFS will allow for early stopping for superiority. The stopping boundaries at the interim and final analyses will be derived based on the exact number of DFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Note that if the target number of events for the interim analysis and final analysis are projected to occur in a shorter time interval (approximately within 6 months), then the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted (statistical significance of only one final analysis of DFS is 0.05 [two-sided]).

If the interim or final DFS monotherapy analysis is significant, the OS monotherapy analysis will be tested hierarchically. The final OS analysis will take place with approximately 182 events among all randomized Part B participants in nivolumab and placebo arms, which is expected to be at approximately 104 months from the start of the study, providing a minimum of 48 months of follow-up. Approximately 182 events are expected, ensuring 44% overall power to detect a HR of 0.73 (P < 0.045). Two formal OS interim monotherapy analyses will be conducted, which will allow for early stopping for superiority. The first and second interim analyses of OS are planned to occur with 102 events (56% of the targeted OS events) and 146 events (80% of the targeted OS events) among the randomized participants in nivolumab and placebo arms, which are expected to be at approximately 76 months and 90 months from the start of the study. Approximately 102 and 146 events are expected providing 8% and 27% power to detect overall interim OS HRs of 0.56 (P < 0.006) and 0.67 (P < 0.023), respectively, at the pre-specified alpha level using the Lan DeMets alpha spending function.

In addition to the formal planned interim analyses for DFS and OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^-$	chloride
CLcr	creatinine clearance
COVID-19	Coronavirus Disease 2019
CNS	central nervous system
CRF	Case Report Form, paper or electronic
ctDNA	circulating tumor DNA
DFS	disease-free survival
DMC	Data monitoring committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EOI-PK	end of infusion-pharmacokinetics
ESR	Expedited Safety Report
FDA	Food and Drug Administration

Term	Definition
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMAE	immune-mediated adverse event
IMP	investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K^+	potassium
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LDH	lactate dehydrogenase
mg	milligram
min	minute

Term	Definition
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
OS	overall survival
PD	pharmacodynamics
PK	pharmacokinetics
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
Tmax, TMAX	time of maximum observed concentration
WBC	white blood cell
WES	whole exome sequencing
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERANCE 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 CRF 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:

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

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

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

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

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

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

Records for study treatments placebo infusions (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

If	Then
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

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

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

MONITORING

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

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

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the site's 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.

CLINICAL STUDY REPORT

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

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

SCIENTIFIC PUBLICATIONS

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

Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resoved.

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).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

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 <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the sudy protocol)[b,c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

• Continuous abstinence must begin at least 30 days prior to initiation of study therapy • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 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
• 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)
Unaccetpatble Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting.

APPENDIX 5 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS [a]	
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, eg, 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

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

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

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

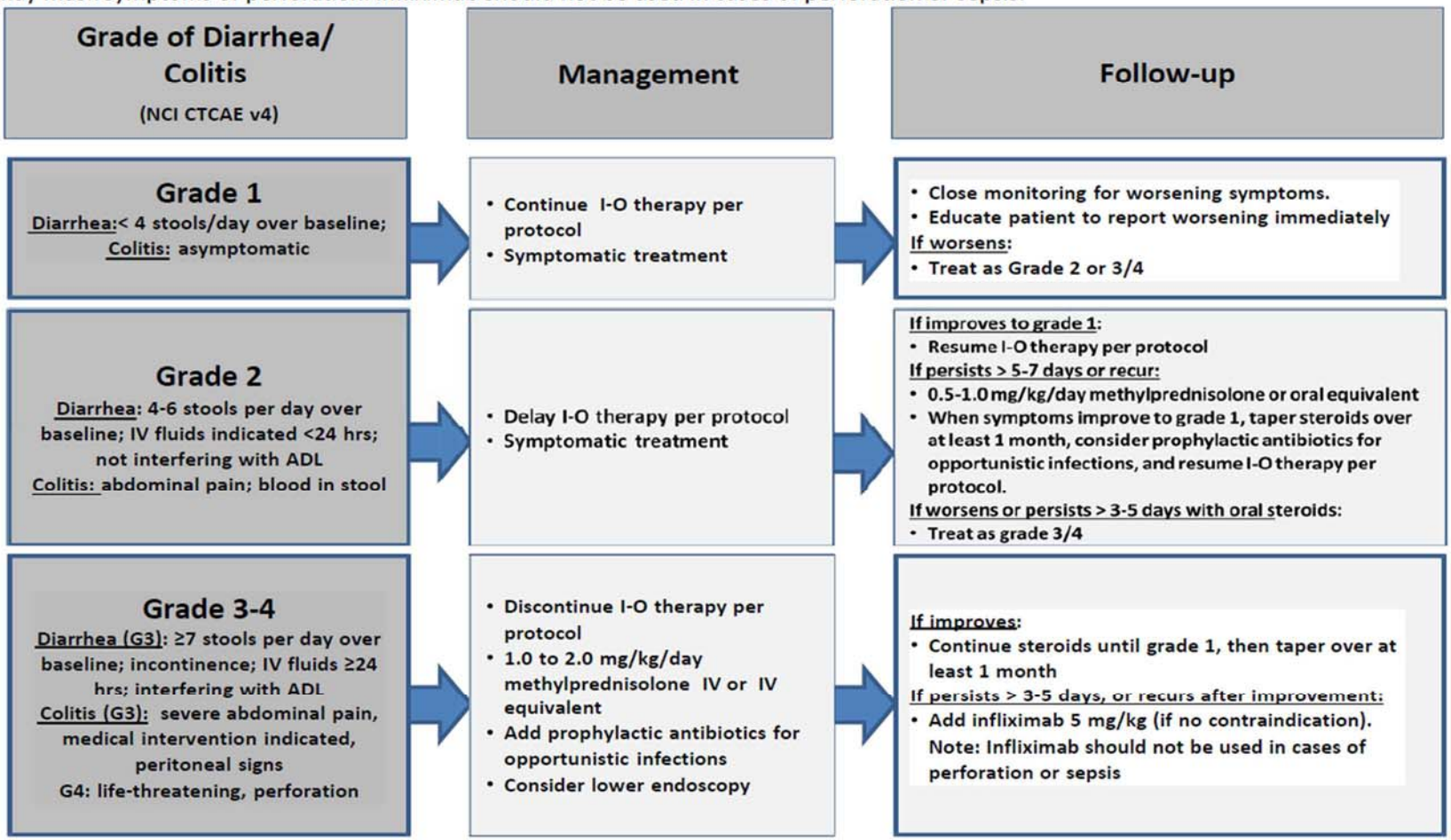
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

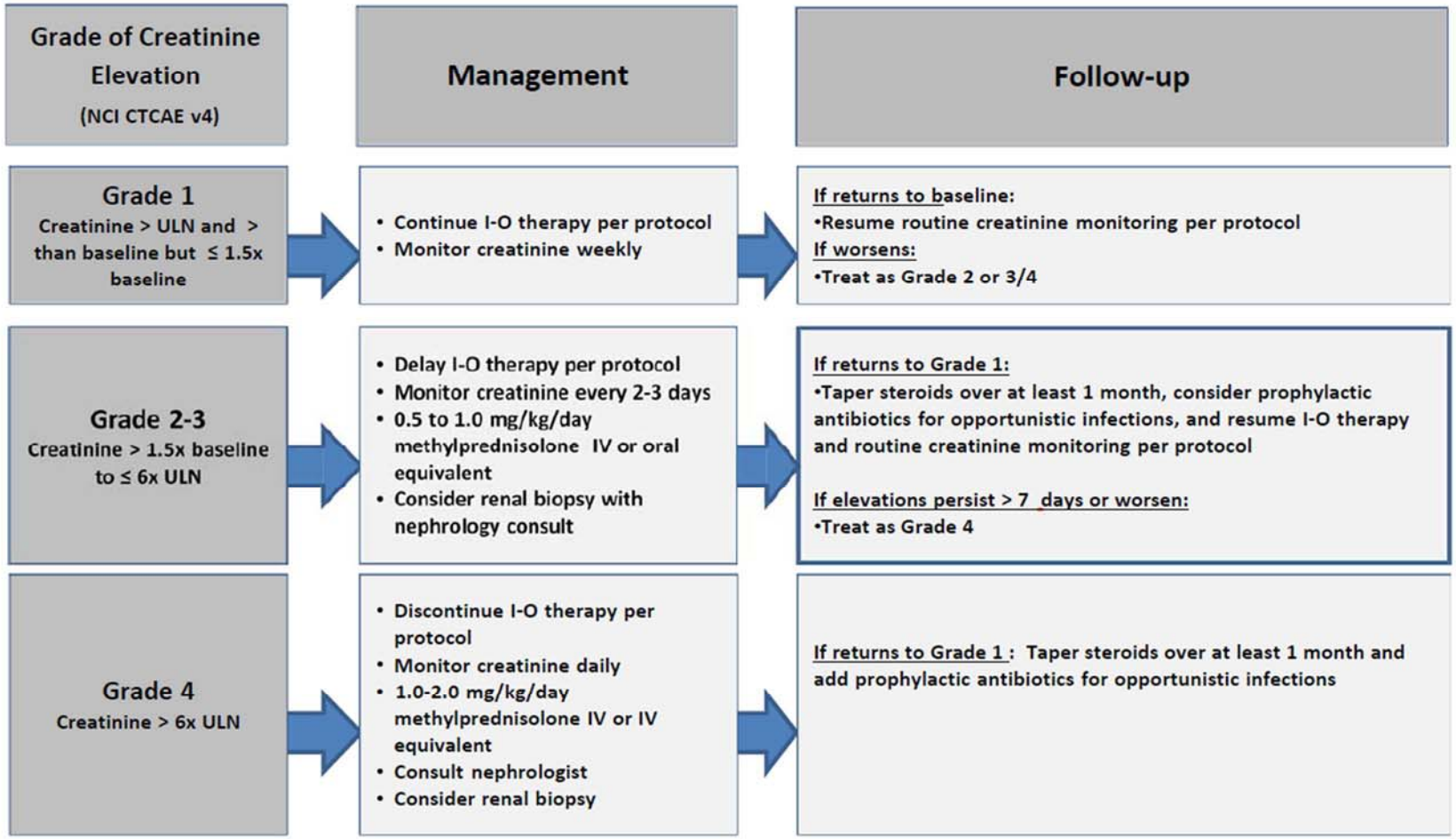


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

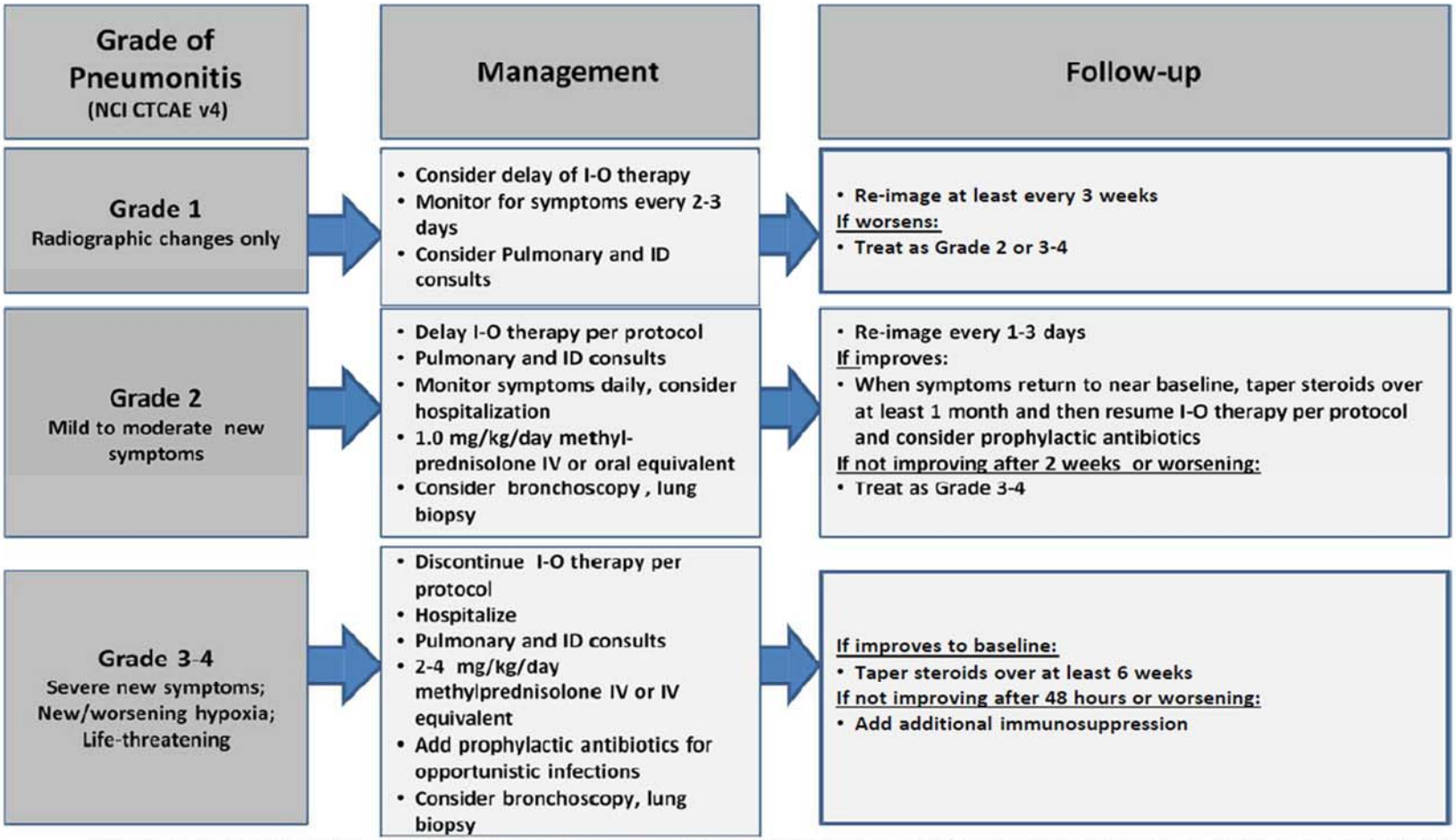


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

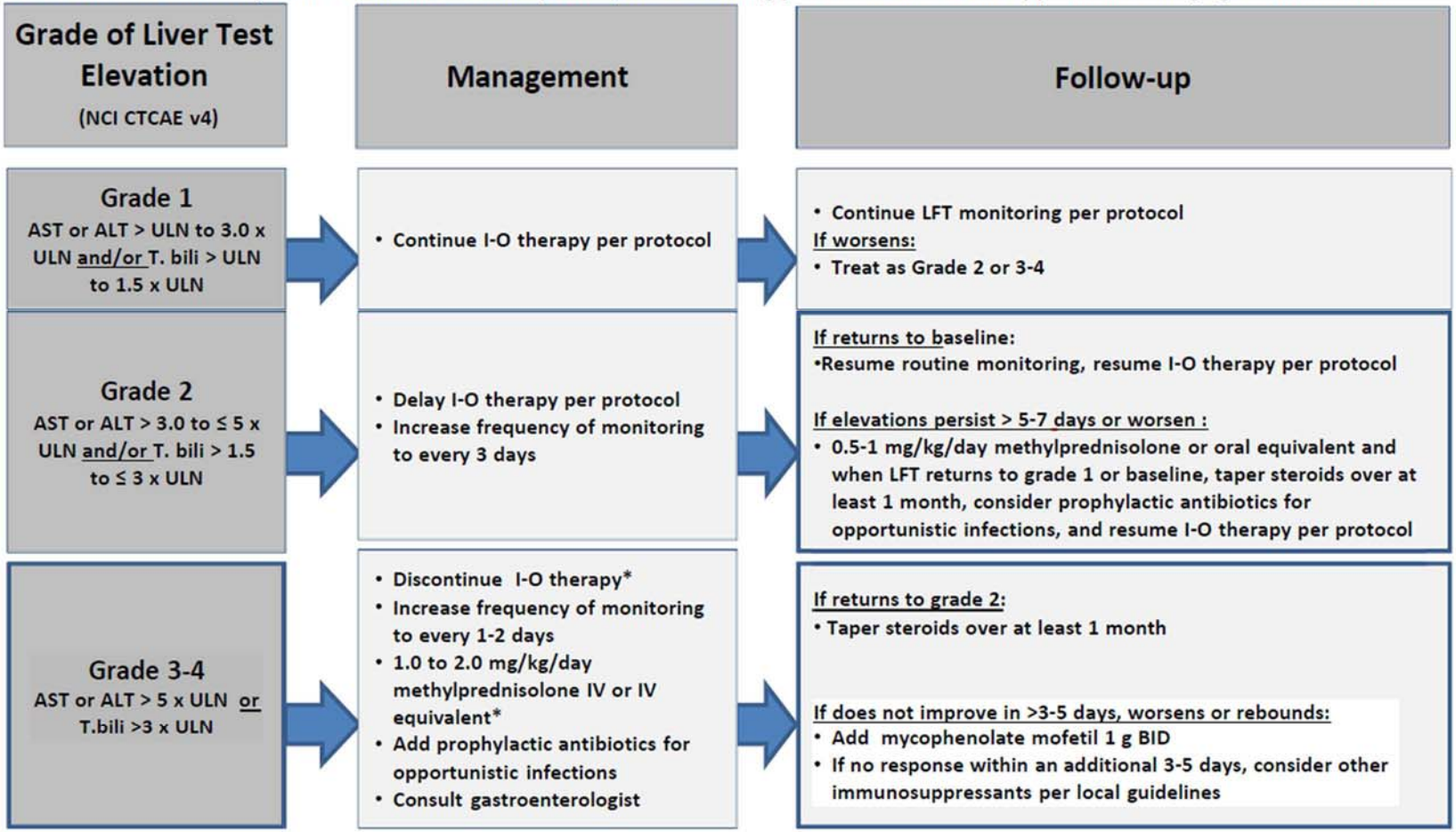


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



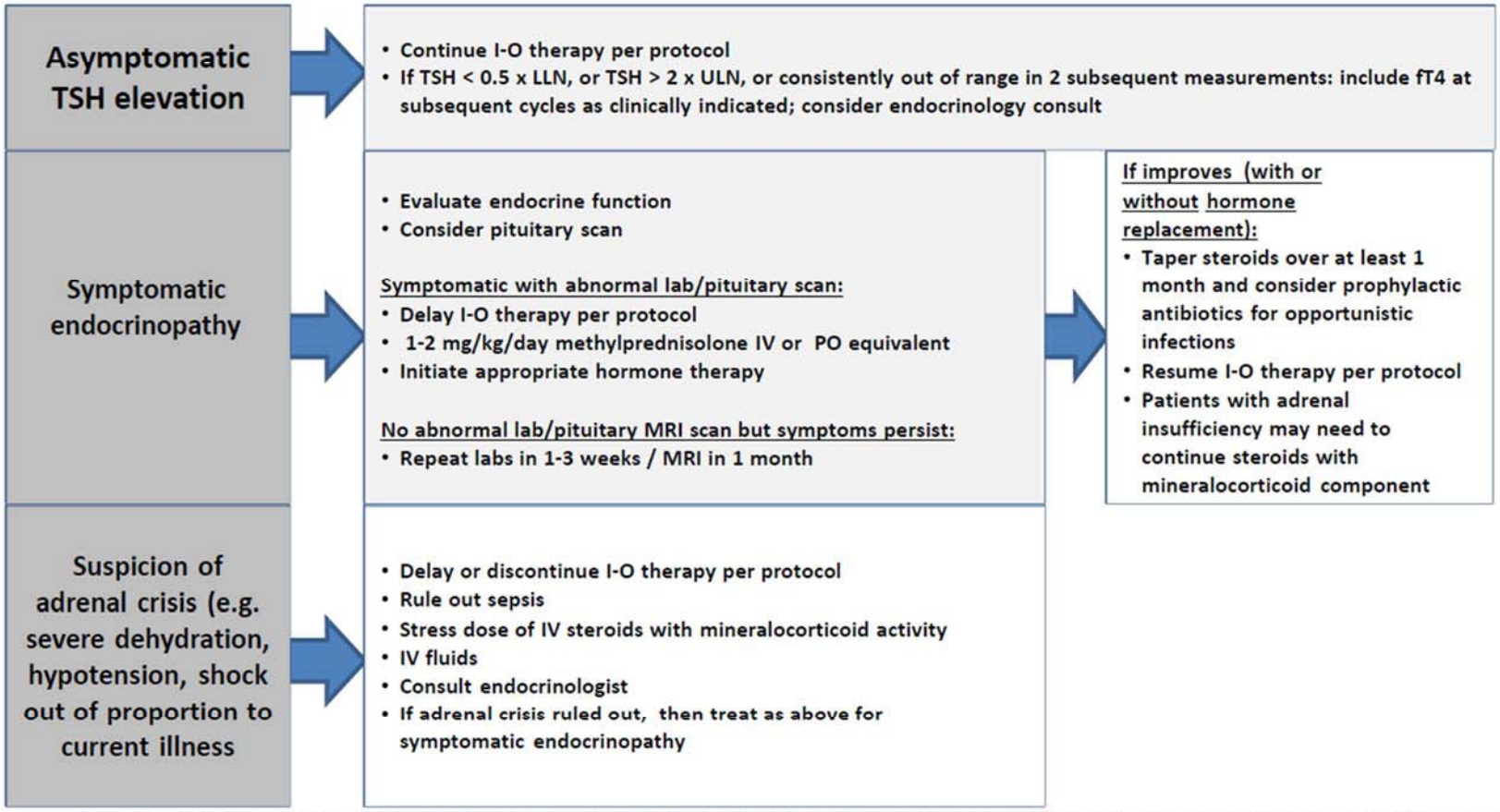
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

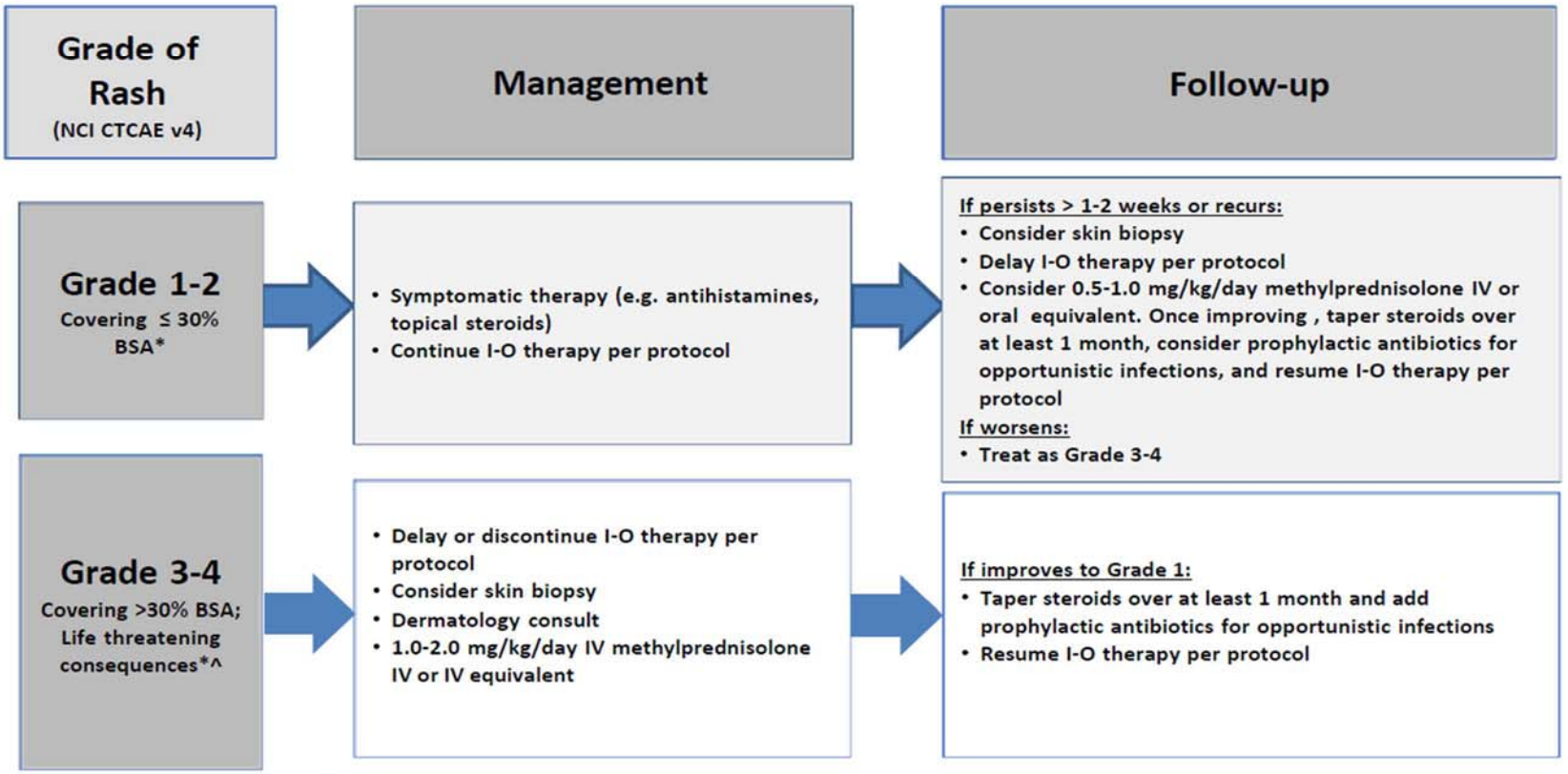


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

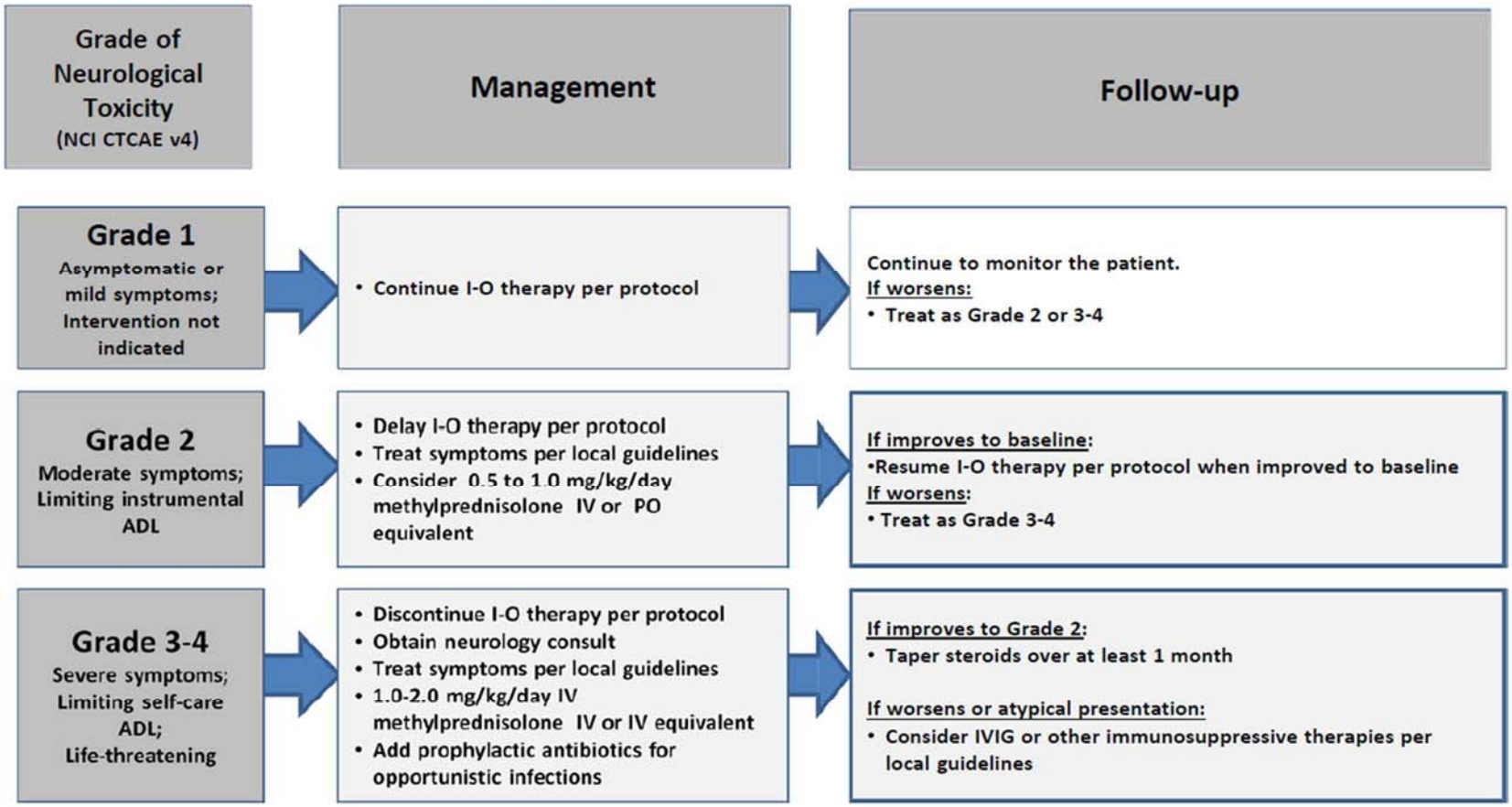
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

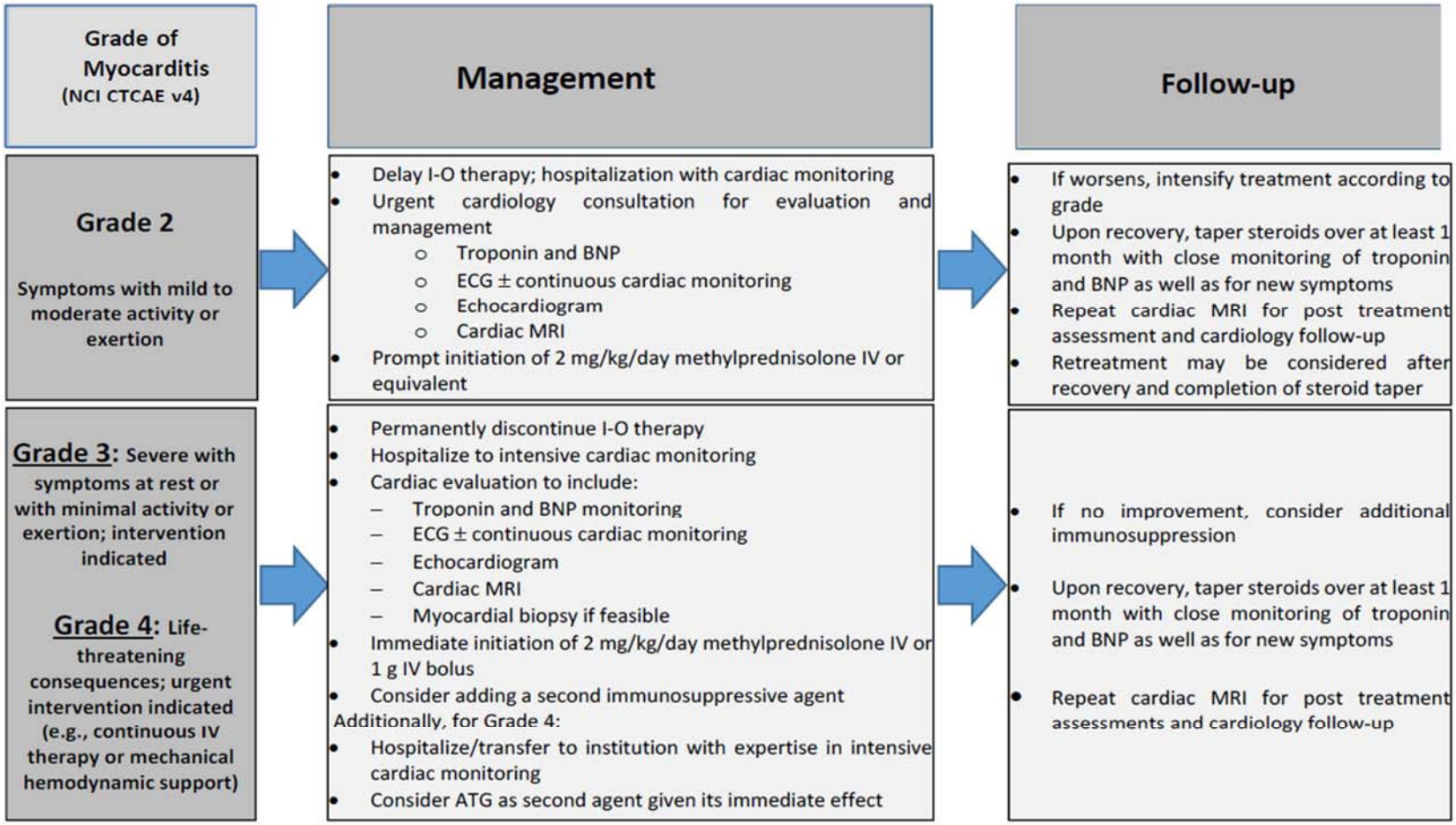
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm



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

28-Sep-2020

APPENDIX 7 COUNTRY-SPECIFIC REQUIREMENTS

Criterion to exclude HIV positive participants <u>where country or local regulations require testing:</u>

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

APPENDIX 8 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 05, 13-Feb-2022

The purpose of Protocol Amendment 05 is to address the timing of interim and final disease-free survival (DFS) analyses in Part A, which were initially planned to occur within 6 months of each other. However, the earlier versions of the protocol did not capture the scenario where in which the interim and final analyses of DFS in Part A occurring in a shorter time interval that could occur in the following instances:

- the number of DFS events needed for final analysis can be observed sooner after observing those needed for interim analysis.
- the total enrollment of both Part A and Part B is expected to be complete closer to the date of DFS final analysis and the criteria to conduct the DFS interim analysis (204 DFS events and enrollment close for the study) is not met.

The amendment is based on the need to address how the formal interim analysis of DFS in Part A would be handled for the above scenario.

With a milestone blinded data transfer received from the BICR vendor through the end of January 2022, BMS observed 202 DFS events in Part A. Because the enrollment in Part B was ongoing (and still ongoing at the time of this amendment), the pre-specified criteria to perform the database lock was not met for conducting the interim analysis of DFS in Part A. Consequently, BMS could not proceed with a database lock for the interim analysis of DFS in Part A. The event projections have showed that the target number of events for final DFS analysis is expected approximately within 4 months from the time of observing the events needed for the interim DFS analysis. Due to these reasons, BMS believes that there are operational challenges to perform an interim and final analysis close to one another. However, the scenario to proceed directly to the final DFS analysis in Part A was not pre-specified in the earlier versions of the protocol. As a result, BMS is issuing a protocol amendment to include this scenario with DFS final analysis only. Table 10.1.1-2 gives details on the alpha, critical hazard ratio, target number of events for the newly added DFS final analysis only scenario in Part A.

This amendment incorporates the changes from the approved Administrative Letters 09 and 10, which are detailed in the Document History but not listed in the Summary of Key Changes below.

Additional revisions, including sections of the protocol synopsis, have been made to align the protocol with respect to these changes. Minor formatting and typographical corrections have been made, therefore have not been summarized.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.1: Part A: Combination Comparison of DFS	Parameters and schedule of analysis for final DFS analysis alone in Part A were added. Also, summary Table 10.1.1-2 was added.	In the event that Part B enrollment is still ongoing at the time of observing the required number of events for the interim analysis and target number of

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 10.1.1-2: Part A Summary of Sample Size Parameters and Schedule of Combination Analysis (without an Interim Analysis) Section 10.3.4: Interim Analyses and Hierarchical Testing		events needed for the final analysis is projected in a shorter time interval (approximately within 4 months), the interim analysis of DFS will not be performed and only one final analysis of DFS will be conducted.
Table 10.1.1-1: Part A Summary of Sample Size Parameters and Schedule of Combination Analyses (with an Interim Analysis)	Table title has been updated and primary analysis population is clarified in the table.	Clarification is provided to reflect the population to be used.
Table 10.1.2-1: Part B Summary of Sample Size Parameters and Schedule of Monotherapy Analyses	Primary analysis population is clarified in the table.	
Table 10.3.1-1: Censoring Scheme Used in Primary Definition of DFS	Text in Situation column of the table was added to include tumor-directed surgery.	To align with the Statistical Analysis Plan.

Overall Rationale for the Revised Protocol 04, 27-Oct-2020

This revised protocol removes Interim Analysis 1 for disease-free survival (DFS), which was scheduled to take place at 43 months for Part A and 68 months for Part B, and delays the remaining interim analysis for DFS from Part A (previously referred to as Interim Analysis 2) from 52 to 56 months, which is the time when the total enrollment is expected to be complete. This will allow for improved follow-up and data maturity for the DFS analyses. For both Part A and Part B, overall survival (OS) will be hierarchically analyzed at the same time as the interim or final analysis for DFS in the same group of subjects. In addition, protocol clarifications and/or updates are provided to sections indicated.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page, document history	Changed the original protocol date to 14-Feb-2017.	This correction was made because Revision 03 had an incorrect original protocol date.
Section 1, Synopsis, Study Population	Added reference to Appendix 9. Added "(a, b, c)" after pT3.	This update was made to better characterize the TNM staging for our study population.
Section 1, Synopsis, Objectives and Endpoints	Added clarification regarding the time periods which will be assessed for safety and tolerability in the objective and endpoint.	These updates were made to clarify the time periods which will be

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		assessed for safety and tolerability in the objective and endpoint.
Section 1, Synopsis, Overall Design	Added clarification surrounding the timing and window permitted for follow up visits.	This update was made to ensure consistency and alignment across the protocol regarding the timing and permitted window for follow up visits.
Section 1, Synopsis, Figure 1 and Figure 2	Updated figures to add "(a, b, c)" after pT3.	This update was made to better characterize the TNM staging for our study population.
Section 1, Synopsis	Added language to clarify the timing and permitted window for follow up visits.	This update was made to ensure consistency and alignment across the protocol regarding the timing and permitted window for follow up visits.
Section 1, Synopsis	Removed list of references.	References were moved from this section of the protocol to the References section
Section 2 Schedule of Activities, Table 2-1	Added note about documentation of vaccine use.	This update was made to ensure appropriate documentation of vaccine use for study participants.
Section 2, Schedule of Activities, Table 2-1	Added a note to Serious Adverse Events Assessment row to include the collection of all AEs (SAEs and non-serious AEs) associated with suspected or confirmed to SARS-CoV-2 infection from time of consent.	Additional criteria for AE assessment was incorporated to include the collection all AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection from time of consent.
Section 2, Schedule of Activities, Table 2-2	Added clarification to AE and SAE Assessment row to include the collection of AEs (SAEs and non-serious AEs) associated with SARS-CoV-2 infection during the treatment period.	All AEs (SAEs and non-serious AEs) associated with SARS-CoV-2 infection should be collected continuously during the treatment period.
Section 2, Schedule of Activities, Table 2-2	Added a note in the laboratory results section regarding the review of laboratory test results that is required prior to each dose.	This note was added to emphasize protocol procedure and requirement outlined in the protocol Section 5.1.
Section 2, Schedule of Activities, Table 2-2	Added clarifying language to ctDNA notes column and removed the notation to collect samples in Cycles 4, 7, & 10 Day 1.	Clarifying language was added to address ctDNA collection alignment with the tumor assessment schedule. The incorrect notation to collect samples in Cycles 4, 7, & 10 Day 1 was removed, as this was entered in error.
Section 2, Schedule of Activities, Table 2-2	Added row for SARS-CoV-2 serology collection. Samples are to be collected at C1D1 and C12D1 for all participants, and	SARS-CoV-2 serology will be collected to assess the impact of SARS-CoV-2 serologic status on

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection.	participants receiving the combination of nivolumab and ipilimumab or nivolumab monotherapy in the adjuvant setting for RCC [redacted]
Section 2, Schedule of Activities, Table 2-3	Outlined the required time period for collection and follow up for SAEs, non-serious AEs of special interest, all AEs (SAEs and non-serious AEs) associated with suspected or confirmed SARS-CoV-2 infection and study treatment-related non-serious AEs.	Additional clarification was provided regarding the follow up for designated AEs in the post-treatment period. The time period for collection for study treatment-related AEs is being extended to better characterize and understand late-onset AEs considered related to study treatment
Section 2, Schedule of Activities, Table 2-3	Added row for ctDNA collection.	An additional ctDNA collection was added in order to align with tumor assessment schedule and to evaluate whether ctDNA is predictive of tumor burden.
Section 2, Schedule of Activities, Table 2-3	Added row for SARS-CoV-2 serology collection. Samples are to be collected at follow-up visit 2 and approximately 4 weeks after a suspected or confirmed SARS-CoV-2 infection.	SARS-CoV-2 serology will be collected to assess the impact of SARS-CoV-2 serologic status on participants receiving the combination of nivolumab and ipilimumab or nivolumab monotherapy in the adjuvant setting for RCC [redacted]
Section 2, Schedule of Activities, Table 2-3	Clarified that timing for scans should be based on date of first treatment, which is considered Week 1.	Language was added to provide clarification regarding tumor assessment schedule calculations to ensure alignment with the study protocol criteria.
Section 2, Schedule of Activities, Table 2-3	Clarified PRO assessment timing in notes column and within footnotes.	Language was added to clarify the timing of PRO assessments.
Section 2, Schedule of Activities, Table 2-3	Updated the footnote regarding timing for follow up visits.	This update was made to ensure consistency and alignment across the protocol regarding the timing and permitted window for follow up visits.
Section 3, Introduction	Updated the text and references within the section.	Text and references were updated to better capture and cite the information provided in the introduction.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3, Introduction, Table 3-1	Added 3 studies.	These 3 studies were included in version 2 of the protocol but were subsequently removed. For consistency purposes, we are including them again in this revision.
Section 4, Objectives and Endpoints, Table 4-1	Added clarification regarding the time periods which will be assessed for safety and tolerability in the secondary objective and endpoint.	These updates were made to clarify the time periods which will be assessed for safety and tolerability in the secondary objective and endpoint.
Section 4, Objectives and Endpoints, Table 4-1	Added an exploratory objective and endpoint to assess the association between the recurrence score with efficacy outcomes.	Gene-signature based score will be assessed in relation to efficacy endpoints.
Section 4, Objectives and Endpoints, Table 4-1	Added an exploratory objective and endpoint regarding SARS-CoV-2 serologic status.	SARS-CoV-2 serology will be collected to assess the impact of SARS-CoV-2 serologic status on participants receiving the combination of nivolumab and ipilimumab or nivolumab monotherapy in the adjuvant setting for RCC [redacted]
Section 4, Objectives and Endpoints, Table 4-1	Added an exploratory objective and endpoint regarding safety of nivolumab combined with ipilimumab and nivolumab monotherapy beyond 100 days and up to 1 year of last dose of study therapy.	Safety information will be collected for study treatment-related AEs beyond 100 days and up to 1 year of last dose of study therapy.
Section 5.1, Overall Design, Figure 5.1-1 and Figure 5.1-2	Updated figures to add "(a, b, c)" after pT3. Removed "Original" from Figure 5.1-1 title.	This update was made to better characterize the TNM staging for our study population.
Section 5.1, Overall Design	Added language about BICR recurrence assessment process.	Language was added to provide guidance on requesting BICR assessment of recurrence and for when there is a discrepancy between the Investigator and the BICR recurrence interpretation.
Section 5.1, Overall Design	Added clarifying language regarding the timing and permitted window for follow up visits.	This update was made to ensure consistency and alignment across the protocol regarding the timing and permitted window for follow up visits.
Section 5.4.1, Rationale for Selection of Participants at Moderate to High Risk of Relapse	Added a potential efficacy assessment using the SSIGN score.	SSIGN score assessments may be performed to identify SSIGN intermediate and high score subgroups.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1, Inclusion Criteria	Added reference to Appendix 9. Added "(a, b, c)" after pT3.	This update was made to better characterize and align the TNM staging for our study population.
Section 6.1, Inclusion Criteria	Added a note regarding the assessment of disease status for participants being considered to enter the study.	This note was added to ensure the safety of the participants, as a participant should not be consented or enrolled into the study if the Investigator is not certain the participant is disease free.
Section 6.1, Inclusion Criteria	The following updates were made: • Added sub criteria (i,ii, and iii) to Criterion 3b) • Added clarification to Criterion 3c • Added clarification to Criterion 3d) and added sub criteria (i,ii, iii, and iv) to Criteria 3d) • Criterion 3e) is no longer applicable • The first sentence in Criterion 3f) is no longer applicable (the second sentence pertaining to WOCBP is still applicable) • Removed text related to male contraception in the last paragraph and added a statement regarding transmission of study drug to a developing fetus	These changes were made to: • Provide clarification and additional details regarding inclusion and contraception requirements for both WOCBP and for women who are not of childbearing potential • Remove contraceptive requirements for male participants based on current safety information
Section 6.2, Exclusion Criteria	Added a note about enrollment of patients with past nephrectomy or other surgical procedure.	This note was added to better clarify the exclusion of patients with a history of RCC and who have been considered cured after a nephrectomy or other surgical procedure in the past and now present with a new RCC.
Section 6.2, Exclusion Criteria	Added a note regarding the use of inactivated vaccines.	Clarification was added regarding the use of inactivated vaccines.
Section 6.2, Exclusion Criteria	Added a criterion regarding SARS-CoV-2 infection.	This exclusion criterion was added to exclude participants with SARS-CoV-2 infection (either suspected or confirmed) within 4 weeks prior to screening.
Section 6.2, Exclusion Criteria	Revised the criterion regarding the use of botanical preparations.	This exclusion criterion was revised to provide clarification regarding the complementary medications that are not permitted within 2 weeks prior to first study treatment.
Section 6.2, Exclusion Criteria	Added a criterion regarding participation in other interventional trials, including those for COVID-19, and receipt of an investigational	This exclusion criterion was added regarding participation in interventional trials, including those

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19.	for COVID-19, and receipt of an investigational SARS-CoV-2 vaccine or other investigational product designed to treat or prevent COVID-19.
Section 6.4.1, Retesting During Screening or Lead-In Period	Added statement regarding re-enrollment, specifically that this study permits the reenrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized/has not been treated).	This statement was re-introduced in the protocol as it was inadvertently removed in Revised Protocol 02.
Section 6.4.1, Retesting During Screening or Lead-In Period	Added criteria regarding SARS-CoV-2 infection.	Language was added to provide guidance for SARS-CoV-2 testing and for when participants develop suspected or confirmed SARS-CoV-2 infection during the screening period.
Section 7.1.1, Administration and Table 7.1.1-2	Added clarifying language regarding the duration of infusion and time between infusions within the section and in the footnote of the table. A statement was also added indicating that simultaneous infusions of nivolumab and ipilimumab will not be permitted.	Language was added to clarify and emphasize study drug administration requirements and expectations.
Section 7.1.1.1, Nivolumab	Added clarifying language regarding the duration of infusion.	Language was added to clarify study drug administration requirements and expectations.
Section 7.1.1.2, Ipilimumab	Added clarifying language regarding the duration of infusion.	Language was added to clarify study drug administration requirements and expectations.
Section 7.2, Method of Treatment Assignment	Added reference to Appendix 9.	This update was made to better align the TNM staging for our study population.
Section 7.3.1 Unblinding at the Time of Disease Recurrence	Added guidance regarding the timing of the request for unblinding if a tumor biopsy collection at the time of suspected recurrence is planned.	This statement was added to provide additional guidance surrounding the unblinding process.
Section 7.4.1, Dose Delay Criteria for Study Treatment	Added Arm C to list of study arms.	Update was made to align with study design.
Section 7.4.1, Dose Delay Criteria for Study Treatment	Added a criterion for dose delay regarding SARS-CoV-2 infection.	SARS-CoV-2 infection (either suspected or confirmed) will meet criteria for dose delay.
Section 7.4.2, Criteria to Resume Treatment	Added criteria required to resume treatment following SARS-CoV-2 infection.	All criteria indicated regarding the SARS-CoV-2 infection must be met to resume treatment.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1, Prohibited and/or Restricted Treatments	Revised the statement regarding the use of botanical preparations.	This language was revised to provide clarification regarding the complementary medications that are not permitted during the study.
Section 7.7.1, Prohibited and/or Restricted Treatments	Added a statement regarding live/attenuated vaccines and inactivated vaccines during the treatment period.	This text was added to better clarify the prohibited and/or restricted treatments for participants enrolled in the study.
Section 9.1.3.2, Investigator Assessment of Recurrence	Clarified that timing for scans should be based on date of first treatment, which is considered Week 1.	Language was added to provide clarification regarding tumor assessment schedule calculations to ensure alignment with the study protocol criteria.
Section 9.1.3.3, BICR Assessment of Recurrence	Updated language regarding the de-identification of relevant cytology/pathology results that support a diagnosis of recurrence.	Language was added to provide guidance on the BICR recurrence assessment process.
Section 9.1.5, Outcomes Research Assessments	Added a statement to indicate that patient-reported outcome assessments should be completed prior to study-related procedures.	Clarification was provided regarding the timing of patient-reported outcome assessments in regards to other study-related procedures.
Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Outlined the required time period for collection for AEs associated with SARS-CoV-2 and those non-serious AEs considered related to study therapy.	Time period for collection of SARS-CoV-2 infection-related events has been added. The time period to collect information regarding AEs considered related to study therapy has been extended to better characterize and understand late-onset AEs considered related to study treatment. This will provide important safety data in the adjuvant setting and better understand the safety profile.
Section 9.2.3, Follow-up of AEs and SAEs	Outlined the required time period for collection for AEs associated with SARS-CoV-2 and those non-serious AEs considered related to study therapy.	Follow up expectations for SARS-CoV-2 infection-related events for those considered related to study therapy have been added.
Section 9.5, Pharmacokinetics; Table 9.5-1	Revised the language regarding the timing for follow-up samples.	This revision was made to ensure consistency and alignment across the protocol regarding the timing and permitted window for follow up visits.
Section 9.5, Pharmacokinetics; Table 9.5-1	Updated the footnote regarding the end of infusion-PK sampling timing.	This footnote was updated to better clarify the timing on end of infusionPK sampling.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8, Biomarkers	Added a description and Table 9.8.1 to summarize the biomarker sampling schedule and requirements for the study.	Description and Table 9.8.1 were added to add clarification regarding the biomarker sampling schedule and requirements for the study.
Section 9.8.1, Additional Research Collection	Added and updaed information about sample collection and storage.	Updated information regarding sample collection and storage was provided.
Section 9.8.1, Additional Research Collection, Table 9.8.1-1	Revised the information in table regarding tumor biopsy sample.	This revision was made to add clarification regarding the additional research sampling schedule the study.
Section 9.8.2, Tissue Specimens	Added a statement indicating that tumor samples will be used for assessment of tumor recurrence score based on gene signature analysis.	Gene signature analysis will be performed on tumor samples to predict the risk of recurrence of the tumor.
Section 9.8.7, Whole Blood for Genotyping	Added language to support whole exome sequencing assessment on whole blood samples.	Statement was added to allow a whole exome sequencing assessment to be performed on whole blood samples.
Section 9.8.8 Immunogenicity Assessments	Added reference to Table 9.5-1.	This reference was added because the immunogenicity sampling schedule is provided in Table 9.5-1.
Section 9.8.9, Other Assessments	Added language on samples collected to assess SARS-CoV-2 serologic status.	Serum will be collected for potential future measurements of anti-SARSCoV-2 antibodies by serology (anti SARS CoV-2 total and immunoglobulin G [IgG]) to explore potential association with safety, efficacy, and/or immune biomarkers.
Section 10.1.1, Part A: Combination Comparison of DFS	Removed 1 interim analysis for DFS. Updated Table 10.1.1-1.	Interim Analysis 1 for the combination comparison of DFS was removed and the remaining interim analysis for DFS from Part A was delayed to allow for improved follow-up and data maturity for the DFS analyses and to align with the timing when enrollment is expected to be complete. OS hierarchical combination analyses aligned with DFS combination analyses. Table was updated to reflect the removal of Interim Analysis 1.
Section 10.1.2, Part B: Monotherapy Comparison of DFS	Removed 1 interim analysis for DFS. Updated Table 10.1.2-1.	Interim Analysis 1 for the monotherapy comparison of DFS was removed from Part B to allow for improved follow-up and data maturity

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		for the DFS analyses. OS hierarchical monotherapy analyses aligned with DFS monotherapy analyses. Table was updated to reflect the removal of Interim Analysis 1.
Section 10.3.4, Interim Analyses and Hierarchical Testing	Added details surrounding the hierarchical overall survival (OS) analysis, for both Part A and Part B, at the same time as the interim or final analysis for DFS in the same group of subjects.	Details were added regarding the alignment of the OS hierarchical monotherapy analyses with DFS monotherapy analyses.
Appendix 2, Study Governance Considerations	Updated appendix.	This appendix was updated to align with the most recent Protocol Model Document.
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	Updated appendix.	This appendix was updated to align with the most recent Protocol Model Document.
Appendix 9, Correlations of Classifications in Cancer Staging Systems	Added appendix.	This appendix was added to address correlations of classifications across cancer staging systems used in this study.
Throughout Document	Updated “patient” terminology to “participant” throughout the document, where applicable.	This update was made to ensure alignment and consistency regarding terminology throughout the document.

Overall Rationale for the Revised Protocol 03, 01-Nov-2019

As the treatment of RCC landscape continues to evolve, accumulative evidence showed a single-agent activity for anti-PD-1 or anti-PD-L1 monotherapy in the 1L treatment of advanced RCC. Single-agent activity of anti-PD1 in the 1L metastatic setting supports the evaluation of nivolumab as monotherapy.

The original study design of the study will remain unchanged and will be designated as Part A of the study. The addition of a monotherapy arm in Part B of the study allows for assessment of the clinical benefit, as measured by disease free survival (DFS) with OS as a key secondary endpoint, provided by nivolumab monotherapy and the contribution of ipilimumab to the benefit observed with combination therapy. If the safety profile is acceptable and nivolumab monotherapy or nivolumab combined with ipilimumab is shown to improve DFS, this study would support the approval of nivolumab or nivolumab combined with ipilimumab in treatment-naive advanced RCC participants post-surgery.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Table 2-2 On-Treatment Procedural Outline	ctDNA collection added	To explore utility as a biomarker associated with clinical efficacy (less invasive than tumor biopsy)
Section 2, Table 2-3	Clarified that anti-tumor therapies are to be collected in survival follow up. Clarification added on timing of PRO collection during follow-up and survival	To clarify language To clarify language and to collect long-term PRO assessments
Section 3, Table 3-1	Updated with most recent listing, and data from clinical trials	Update was done to provide the most recent data and keep the protocol current
Section 3.1, Study Rationale	Updated to provide rationale for inclusion of the Part B treatment into the study design.	To elucidate on the rationale for including a Part B into the study
Section 3.1.1 Research Hypothesis	Updated to reflect in the addition of Part B into the study.	Incorporation of Part B provides
Section 3.2.1.1	Updated background information on nivolumab in RCC was added.	Incorporate recent data on monotherapy in the RCC setting and also combination therapy with ipilimumab.
Section 3.3 Benefit/Risk Assessment	Updated to include discussion of nivolumab monotherapy	To elucidate on the benefit/risk assessment for including a Part B into the study
Section 4 Objectives	Revised to include the objectives for Part B of the study.	Primary and secondary objectives were updated to incorporation Part B of the study.
Section 5.1 Overall Design	Updated to reflect incorporation Part B in the study design: updated number of participants, randomization arms, and schema	Updated with the details of Part B.
Section 5.2, Number of Participants	Updated the number of participants to account for Part A and Part B of the new study design.	The sample size was increased for incorporation of Part B.
Section 5.4.4, Rationale for Nivolumab Monotherapy	Rationale for the addition of the Part B study added.	To elucidate on the rationale for the addition of the new monotherapy arm in Part B.
Section 5.5.2, Justification for Dose of Nivolumab Monotherapy Treatment Added.	Updated to incorporate justification for nivolumab 240 mg as monotherapy.	To elucidate on the dosing justification on the new monotherapy arm
Section 6.2, Exclusion Criteria	Added exclusion criteria for participants that have received a live vaccine within 30 days of first dose.	Update was made to reflect the current program-level exclusion criteria

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1, Table 7.1.1-2 Dosing Schedule	Added treatment for each cycle for Arm C in Part B.	To provide dosing details on the new monotherapy arm, Arm C in Part B.
Section 7.7.3 Permitted therapy	Added a statement to indicate that concomitant medications are also to be recorded in the appropriate section of the CRF within 100 days of the last dose date of study drug	To clarify when concomitant medications are to be recorded during the study
Section 9.1.5 Outcomes Research Assessment	Clarified description of FKSI-19.	To add more granularity on the FKSI-19 description
Section 9.2.9 Management Algorithms	Added myocarditis algorithm	Update was made to reflect the current program-level myocarditis algorithm
Section 9.8.6 Peripheral Blood DNA Mutation Research	Added for collection of ctDNA	To explore utility as a biomarker associated with clinical efficacy (less invasive than tumor biopsy)
Section 10.1 Sample Size Determination; Section 10.1.2 Monotherapy Comparison of DFS	Sample Size section was updated to reflect sample size determinations for Part A and B.	Part A remains intact as the original design, Part B determinations were added (Section 10.1.2) to reflect determination of sample size for monotherapy comparison of DFS.
Section 10.1.3 Contribution of Components Analysis of DFS	CoC description added.	CoC description and timing added to the protocol.
Section 10.2, Populations for Analyses	Populations for Part B analyses have been added.	To reflect the additional populations for analyses in Part B.
Section 10.3.3.3 Outcomes Research Analyses	Updated to include clarification of analyses Updated to include nivolumab vs placebo comparisons.	To clarify intended outcome research analyses
Section 10.3.4 Interim Analyses and Hierarchical Testing	Updated to include interim analyses for Part A and B, and to include description of hierarchical testing	To clarify intended interim analyses, and hierarchal testing that will occur for the OS interim analysis.

Overall Rationale for the Revised Protocol 02, 06-Apr-2018

The purpose of this revised protocol is to reduce frequency of patient questionnaires, update exclusion criteria 3f for serum creatinine, and provide additional information and/or clarification to sections indicated. Typographical and grammatical errors were also corrected.

This applies to all sites and all patients. The changes in this amendment do not impact the safety of participants and should be implemented after Institutional Review Board or Ethics Committee review.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Medical Monitor info updated.	As per Administrative Letter
Synopsis Key Inclusion Criteria (Item a); 6.1 (Item 2a)	Wording updated to indicate clean surgical margins are required for all patients and clarified timing of nephrectomy.	Clarification of criteria
Synopsis Key Inclusion Criteria (Item d); 6.1 (Item 2d)	"(post-operative)" was added in NOTE: "...on the baseline (post-operative) tumor assessment..."	To clarify that this refers to the post-operative baseline assessment.
Synopsis Overall Design; 5.1 Overall Design	Changed wording regarding duration of time between nephrectomy and randomization (greater than 4 weeks and less than or equal to 12 weeks).	Clarification
Figures 1-1 and 5.1-1	Updated study schema was inserted.	Ease of viewing
Table 2-1	42-day screening window removed.	Randomization must occur within 12 weeks of surgery which provides for an end of screening timepoint.
Table 2-1 Lab test; Appendix 7 Country-Specific Requirements	Replaced Germany with "country or local regulations" where HIV testing required.	Appendix provides information regarding screening and exclusion criteria related to HIV testing.
Table 2.2 Patient Reported Outcomes	• Decreased frequency of questionnaires. • Added footnote c indicating that Question GP5 on FSKI-19 can be left blank at baseline.	• Decrease need for patient to complete and will provide sufficient timepoints for evaluation. • Participant has not received treatment yet and question asks if patient is bothered by side effects of treatment.
Table 2.3 Tumor Assessments	Updated allowable windows for scans.	Provide more flexibility in scheduling Q6 month and yearly scans.
Table 2.3 Tumor Assessments; 9.1.3.2 Investigator Assessment of Recurrence	Added bullet that tumor assessments can be discontinued when recurrence has been confirmed by BICR.	Clarification to avoid confusion.
Table 2.3 Patient Reported Outcomes	• Updated information for collection. • Added footnotes c and d to clarify that PROs can be performed via telephone and timing for recurred patients to obtain questionnaires.	Clarify timing in survival follow-up.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
3 Introduction; 11 References	Second to last paragraph added information regarding sunitinib approval in adjuvant in US, including a reference to updated NCCN guidelines.	Provide data regarding US approval.
Table 3-1, PROTECT	Updated outcome measure for PROTECT study.	Provided update since study completed.
3.2.1.3 Nivolumab plus Ipilimumab in RCC; Tables 3.2.1.3-1, 3.2.1.3-3, 3.2.1.3-4	Added information regarding results of CA209-214 - nivolumab plus ipilimumab in first line RCC	Provide information regarding combination studies and results.
5.1 Overall Design	• Changed wording regarding duration of time between nephrectomy and randomization (greater than 4 weeks and less than or equal to 12 weeks). • Removed info related to 42-day screening period and re-enrollment. • Added clarifications on repeat labs during screening.	Clarification
6.1 Inclusion Criteria	• Item 2a wording updated to indicate clean surgical margins are required for all patients and clarified timing of nephrectomy. • Item 2c related to N1 status added further language indicating one or more regional lymph nodes having positive results. • Item 2d (post-operative) was added in NOTE: ....on the baseline (post-operative) tumor assessment ...	• Clarification of criteria • Clarification of criteria • To clarify that this refers to the post-operative baseline assessment
6.2 Exclusion Criteria	• Item 1a Germany removed and language updated to include all countries and locals where testing is mandated • Item 2c added regarding the exclusion of treatment with botanical preparations • Item 3f changed to exclude for serum creatinine of >1.5 x ULN unless creatinine clearance is ≥ 40 ml/min	• Clarify exclusion of HIV positive participants in areas where testing is mandated. • Nivolumab program language • Updated to reflect standard used in program allowing participants with adequate clearance to participate
6.4.1 Retesting During Screening	Removed first paragraph regarding re-enrollment	Paragraph did not apply to retesting
7 Treatment; 7.1.1 Administration; 7.1.1.2 Ipilimumab	Added percentages to IMP injection solution	Clarification and consistency

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.1.1 Administration	Updated language in last two full paragraphs	Clarification
Table 7.1.1-1	Revised table title to better reflect contents	Clarification
Table 7.1.1-2	Added note indicating approximately 30 minutes between nivolumab and ipilimumab infusions	Reminder/clarification
7.1.1.1 Nivolumab	Referred reader to IB for additional instructions on preparation.	Additional instruction
7.1.1.2 Ipilimumab	Added language regarding approximate 30 minute between nivolumab and ipilimumab	Reminder/clarification
7.2 Method of Treatment Assignment	Added date of nephrectomy to bulleted list of information required for randomization	Clarification
7.4.1 Dose Delay Criteria for Study Treatment	Added Grade 3 asymptomatic amylase and lipase as not requiring dose delay.	Nivolumab program language
7.4.2 Criteria to Resume Treatment	Added information on allowable systemic corticosteroid doses	Clarification
7.6 Treatment Compliance	Added that source data will be verified by the BMS unblinded site monitor.	Clarification
7.7.1 Prohibited and/or Restricted Treatments	Added bullet that any botanical preparations are prohibited.	Nivolumab program language
7.7.3 Permitted Therapy	Changed wording slightly from "Physiologic replacement doses of systemic corticosteroids... for participants with adrenal insufficiency" to "Adrenal replacement steroid doses..."	Nivolumab program language
8.1.1 Study Treatment Discontinuation Criteria	Re-organized bulleted criteria into events that do require discontinuation and events that do not require discontinuation.	Clarification to avoid confusion.
9.1.2 Methods of Measurement	Revised and expanded CT/MRI text, including details regarding contraindications.	Clarification
9.1.2 Methods of Measurement	Removed references to RECIST	No lesion measurements at baseline so criteria not applicable.
9.1.3.1 Assessment of Baseline Disease-free Status	Changed timing of imaging performed post-nephrectomy from "at least" to "greater than" 4 weeks.	Correction
9.1.3.2 Investigator Assessment of Recurrence	• Removed phrase "for the duration of the disease-free follow-up" from text regarding tumor assessments. • Updated General Considerations and replaced Table 9.1.3.2-1.	• Avoid confusion regarding follow-up assessments.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		• Provide clarifications to criteria used to assess recurrence.
9.1.3.3 BICR Assessment of Recurrence	Additional instruction added.	Clarification
Table 9.1.4-1, Acceptable Imaging Assessment Methods	Added a third alternative method for abdomen and pelvis.	Consistency
9.2.2 Method of Detecting AEs and SAEs	Added text regarding collection and assessment of AEs.	Nivolumab program language
Table 9.5-1 PK and Immunogenicity Sampling Schedule	Added to footnote b regarding the timing of collecting predose samples.	Clarification
Appendix 4 WOCBP and Contraception	Acceptable contraception methods updated to include hormonal methods.	Nivolumab program language
Appendix 7 Response Criteria (RECIST 1.1)	Appendix removed.	RECIST criteria not used in this study.

APPENDIX 9 CORRELATIONS OF CLASSIFICATIONS IN CANCER STAGING SYSTEMS

The CA209-914 study stratification criteria is based on the 2010, 7th edition American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification and Fuhrman grading and therefore, only information on these classification systems should be entered into the database.

The AJCC/UICC TNM (tumor, node, and metastasis) classification on cancer staging systems are regularly updated. The AJCC/UICC 8th edition[1] was implemented in 2018 and it introduces some (minor) staging changes and refines some definitions, but retains most of the 7th edition parameters.[2] Thus, in the new edition, the word "grossly" to describe renal vein and segmental branch invasion has been removed from the T3a, because the 7th edition had over-reliance on the pathologist gross inspection of the hilar vessels. However, tumor involvement of renal vessels can be missed grossly. In addition, for the T3a staging, the statement "Muscle containing" was changed to "segmental branches" and the "Invasion of pelvicalyceal system" was added as this part of the collecting system is within the hilum.

For the purposes of our CA209-914 study conduct, we are maintaining the Tumor staging equivalent between the 2010, 7th edition AJCC/UICC and the 2017, 8th edition AJCC/UICC.[3]

	2010, 7th edition AJCC TNM classification	2017, 8th edition AJCC/ UICC TNM classification
Tx	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney	
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney	
T1b	Tumor > 4 but ≤ 7 cm in greatest dimension, limited to the kidney	
T2	Tumor > 7 cm in greatest dimension, limited to the kidney	
T2a	Tumor >7 cm but ≤ 10 cm in greatest dimension, limited to the kidney	
T2b	Tumor > 10 cm, limited to the kidney	
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia	
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm	Tumor extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (includes contiguous extension into ipsilateral adrenal gland)	

Tumor grade — The AJCC 8th edition adopted the histologic grade (G1–G4) WHO/ISUP nucleolar grading, replacing the traditional Fuhrman nuclear grade.

However, UICC 8E has retained the use of Fuhrman for clear cell RCC and has not adopted the WHO/ISUP nucleolar grade-adopted 8E AJCC.

In the WHO/ISUP histologic grade, the nucleolar grade alone is sufficient to define grades 1 to 3 for clear cell and papillary RCC.[4] Aggressive histologies such as sarcomatoid and rhabdoid differentiation are incorporated into WHO/ISUP grade 4.

Therefore, for the purposes of our CA209-914 study conduct, we are maintaining the histologic-grading equivalent between the Fuhrman and the WHO/ISUP systems.

Comparison of Conventional Four-Tiered Fuhrman Grading and WHO/ISUP Grading System is below[5]:

Grade	Fuhrman Grade System			WHO/ISUP Grading System
	Nuclear Diameter (μm)	Nuclear Shape	Nucleoli	Nucleoli
1	Small (≈10)	Round/ uniform	Absent/ inconspicuous	Absent or inconspicuous and basophilic at ×400 magnification
2	Large (≈15)	Irregular outline	Visible at ×400 magnification	Conspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification
3	Larger (≈20)	Obvious irregular outline	Visible and prominent at ×100 magnification	Conspicuous and eosinophilic at ×100 magnification
4	Grade 3 plus bizarre multilobed nuclei ± spindle cells			Extremely unclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation

References

[1] American Joint Comittee on Cancer. Cancer Staging Manual, 8th Edition Updates and Corrections; 2018. Available from URL: https://cancerstaging.org/references-tools/deskreferences/pages/8eupdates.aspx

[2] Paner GP, Stadler WM, Hansel DE, et al. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. Eur Urol 2018;73(4):560-9.

[3] Cornejo KM, Rice-Stitt T, Wu CL. Updates in staging and reporting of genitourinary malignancies. Arch Pathol Lab Med 2020;144(3):305-19.

[4] Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Grading of clear cell renal cell carcinoma should be based on nucleolar prominence. Am J Surg Pathol 2011;35(8):1134-9.

[5] Samaratunga H, Gianduzzo T, Delahunt B. The ISUP system of staging, grading and classification of renal cell neoplasia. J Kidney Cancer VHL 2014;1(3):26-39.