Official Title of Study:

A Phase 2, Single-arm Open-label Study of Combination Nivolumab and Ipilimumab Retreatment in Advanced Renal Cell Carcinoma Patients Progressing on Nivolumab Maintenance Therapy After Nivolumab and Ipilimumab Induction

(CheckMate 73M: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 73M)

PROTOCOL(S) CA209-73M

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CLINICAL PROTOCOL CA20973M

A Phase 2, Single-arm Open-label Study of Combination Nivolumab and Ipilimumab Retreatment in Advanced Renal Cell Carcinoma Patients Progressing on Nivolumab Maintenance Therapy After Nivolumab and Ipilimumab Induction

(CheckMate 73M: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 73M)

Short Title:

A Study of Combination Nivolumab and Ipilimumab Retreatment in Patients with Advanced Renal Cell Carcinoma

Revised Protocol: 01

Study Director	**Medical Monitor**
[redacted]	

24-hr Emergency Telephone Number
USA: [redacted]
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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	12-Mar-2020	The purpose of this revised protocol is to clarify that the sample collection at progression post-retreatment is optional and may be collected. In addition, this revised protocol includes updates to study personnel; clarification to inclusion criterion for determining progression; clarification to exclusion criteria for adverse event of adrenal insufficiency and HIV criteria for exclusion; and updated language for additional research sample collections.
Original Protocol	25-Apr-2019	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 01:

This revised protocol clarifies that the tumor tissue sample collection at the time of progression during this study, post-retreatment, is optional. In addition, this revised protocol includes updates to study personnel; clarification to inclusion criterion for determining progression; clarification to exclusion criteria for adverse event of adrenal insufficiency and HIV criteria for exclusion; and updated language for additional research sample collections. Changes are listed below in the table.

Revisions apply to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Update Medical Monitor contact information *Original test:* [redacted] *Change to:* [redacted] Update study director contact information *Original text*: [redacted] *Change to:* [redacted]	Update medical monitor name and contact information and update study director contact information.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Key Inclusion Criteria and Section 6.1 Inclusion Criteria	Updated inclusion criterion synopsis, bullet 3 and Section 6.1, 2)c) to the following: Investigator-assessed, per RECIST 1.1, disease progression on nivolumab maintenance after induction with ipilimumab and nivolumab and PR/CR or SD ≥ 6 months after starting initial induction treatment.	Clarify inclusion criterion for determining progression.
Synopsis, Key Inclusion Criteria	Key inclusion criteria, bullet 6 was revised to state "...must be submitted to the central vendor (block or unstained slides) in order to start a participant to study treatment...".	To align key inclusion criteria listed in the Synopsis with the inclusion criteria listed in Section 6.1.
Synopsis, Key Exclusion Criteria	To align the exclusion criterion for serum creatinine in the synopsis with the exclusion criterion in the body.	Reconcile discrepancy between synopsis and body for the exclusion criterion for serum creatinine.
Synopsis, Steering Committee, Section 5.1.1 Steering Committee and other External Committees	Remove the Steering Committee. *Replace with:* No (Synopsis), Not applicable (Section 5.1.1)	To clarify that the study will not have a Steering Committee.
Section 5.1 Overall Design	Add the following statement to the second bullet: with the exception of patients with prior history of adrenal insufficiency that are under control with hormone replacement.	Clarify exclusion criterion for adverse events of adrenal insufficiency that meet criteria for treatment discontinuation.
Section 6.2: Exclusion Criteria	Exclusion criteria 1) b) Add the following statement: with the exception of patients with prior history of adrenal insufficiency that are under	Clarify exclusion criterion for adverse events of adrenal insufficiency that meet criteria for treatment discontinuation.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	control with hormone replacement. Exclusion criteria 1) h) marked as not applicable. Delete: h) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at sites where mandated locally (see Appendix 8). *Change to:* Not applicable per revised protocol 01	Exclusion criteria not applicable.
Section 7, Table 7-1, Study Treatments for CA20973M	Update the following information listed in Table 7-1: Product Description /Class and Dosage Form, Potency, Packaging/Appearance and Storage Conditions	To minimize protocol revisions in the event of a product packaging configuration changes.
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3.2, Safety Analyses	Remove coagulation from secondary statistical analyses	Correction made to reflect actual analysis to be done.
Section 10.3.5 Interim Analysis,	Remove the assessment by the Steering Committee	To remove the assessment of interim reports by the Steering Committee.
Appendix 5 Management Algorithms	Added Myocarditis algorithm and revised date of the other algorithms to 2019.	Provided Myocarditis algorithm per recent Nivolumab Investigator Brochure.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 2, Single-arm, Open-label Study of Combination Nivolumab and Ipilimumab Retreatment in Advanced Renal Cell Carcinoma Patients Progressing on Nivolumab Maintenance Therapy After Nivolumab and Ipilimumab Induction

Short Title:

A Study of Combination Nivolumab and Ipilimumab Retreatment in Patients with Advanced Renal Cell Carcinoma

Study Phase:

2

Rationale:

Tyrosine kinase inhibitors (TKIs) have been the standard of care for metastatic renal cell carcinoma (mRCC) over the past 10 years. In the last few years, immunotherapy has been introduced into the treatment algorithm of mRCC. More recently, the combination of ipilimumab and nivolumab has demonstrated superiority over sunitinib in patients with intermediate and poor risk advanced or metastatic clear cell renal cell carcinoma (RCC). Treatment consists of an induction phase including 4 doses of combination ipilimumab and nivolumab in 3-week intervals followed by a maintenance phase with single agent nivolumab given every 4 weeks. If patients progress on maintenance nivolumab treatment they are switched to second line treatment.

No data exist regarding the retreatment of ipilimumab for patients who show signs of progressive disease on nivolumab maintenance therapy after nivolumab and ipilimumab induction. Stimulation of an immune response by reintroducing ipilimumab and nivolumab could regain tumor control.

Research Hypothesis:

Retreatment with ipilimumab in combination with nivolumab in patients progressing on nivolumab maintenance therapy after ipilimumab and nivolumab induction, will result in improved clinical benefits based on disease control rate (DCR).

Study Population:

Adult participants (≥ 18 years) with histologically confirmed RCC with a clear-cell component who have progressed on nivolumab maintenance after induction with combination nivolumab and ipilimumab.

Key Inclusion Criteria:

- Advanced (not amenable to curative surgery or radiation therapy) or metastatic (American Joint Committee on Cancer Stage IV) RCC
- Histological confirmation of RCC with a clear-cell component, including participants who may have sarcomatoid features
- Investigator-assessed, per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), disease progression on nivolumab maintenance after induction with ipilimumab and

nivolumab and partial response (PR)/complete response (CR) or stable disease (SD) ≥ 6 months after starting initial induction treatment.

- Measurable disease by computed tomography or magnetic resonance imaging per RECIST 1.1 criteria
- Karnofsky Performance Status of at least 70% or higher
- Tumor tissue (formalin-fixed paraffin-embedded [FFPE] archival prior to the first treatment and recently acquired at or after progression on initial nivolumab maintenance) must be submitted to the central vendor (block or unstained slides) in order to start a participant to study treatment. (Note: Fine needle aspiration and bone metastases samples are not acceptable for submission.)

Key Exclusion Criteria:

- Any prior adverse event that meets the criteria for treatment discontinuation
- Any 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 (eg, celiac disease) are permitted to enroll.
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
- Uncontrolled adrenal insufficiency
- Participants with human immunodeficiency virus (HIV) infections are excluded if any of the following applies:
  a) CD4+ T-cell count < 350 cells/μL
  b) Any acquired immunodeficiency syndrome-defining opportunistic infection occurred in the last 12 months
  c) HIV viral load is ≥ 400 copies/mL
  d) Antiretroviral therapy has been administered at current doses for less than 4 weeks
  e) The participant is not on antiretroviral therapy
- Participants with a history of chronic hepatitis B or C are excluded if any of the following applies:
  a) For participants with chronic hepatitis B: The HBV viral load is detectable.
  b) For participants with chronic hepatitis C: The HCV viral load is detectable.
- Known medical, emotional, psychiatric, or logistical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study treatment.

- Presence of any toxicities attributed to prior anticancer therapy, other than alopecia, that have not resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) or baseline before administration of study treatment
- Any of the following laboratory test findings:
  a) White blood cells < 2,000/µL
  b) Neutrophils < 1,500/µL
  c) Platelets < 100,000/µL
  d) Serum creatinine > 1.5× upper limit of normal (ULN) unless calculated creatinine clearance (CrCl) ≥ 40 mL/min (measured or calculated by Cockroft-Gault formula).
  e) Aspartate aminotransferase or Alanine aminotransferase > 3× ULN [> 5× ULN if liver metastases are present])
  f) Total bilirubin (TBili) > 1.5× ULN (except participants with Gilbert syndrome, who must have TBili < 3.0× ULN)

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To describe the efficacy in terms of DCR of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• DCR is defined as the proportion of participants who achieve a confirmed best response of CR, PR, or SD for at least 6 months after first treatment dose using the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) criteria.
Secondary	
• To describe the overall survival (OS) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• OS is defined as the time from first dose to the date of death from any cause. For participants that are alive, their survival time will be censored at the date of last contact ("last known alive date"). OS will be censored for participants at the date of first dose if they were treated but had no follow-up.
• To describe the objective response rate (ORR) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• ORR is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST 1.1 criteria.
• To describe the duration of response (DOR) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression, per RECIST 1.1 criteria, or death due to any cause, whichever occurs first.
• To describe the progression-free survival (PFS) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• PFS is defined as the time between the date of first dose and the first date of documented progression, as per RECIST 1.1 criteria or death due to any cause, whichever occurs first.

Objective	Endpoint
• To describe the time to objective response (TTR) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• TTR is defined as the time between the date of the first dose and the first confirmed documented response (CR or PR) per RECIST 1.1 criteria.
• To estimate the incidence of adverse events (AEs) of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• AE incident rate is defined as the proportion of participants with any grade AEs. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.

Overall Design:

This is a Phase 2, open-label, single-arm study divided into 2 parts. A Simon 2-stage design will be used.

- In Stage 1, 27 response-evaluable patients will be enrolled and a futility analysis will be performed.
- In Stage 2 (if Stage 1 is positive), 53 more response-evaluable patients will be enrolled.

Number of Participants:

Approximately 96 participants will be enrolled in order to obtain 80 response-evaluable patients, accounting for approximatively 20% of non-evaluable patients or withdrawal. The number of enrolled participants with SD ≥ 6 months will be capped at 50%.

A Simon 2-stage design will be used to test whether retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilumumab and nivolumab yields a DCR that is of clinical interest. In this study, a DCR in excess of 20% will be considered of clinical interest. The Simon design will test the null hypothesis that the true DCR is less than or equal to 20% versus the alternative hypothesis that it exceeds 20%. The type I error rate will be 5% and the design will have 85% power to reject the null hypothesis when the true DCR is 35%.

Treatment Arms and Duration:

Study treatment includes Investigational [Medicinal] Products (IP/IMP) as indicated in Table 1.

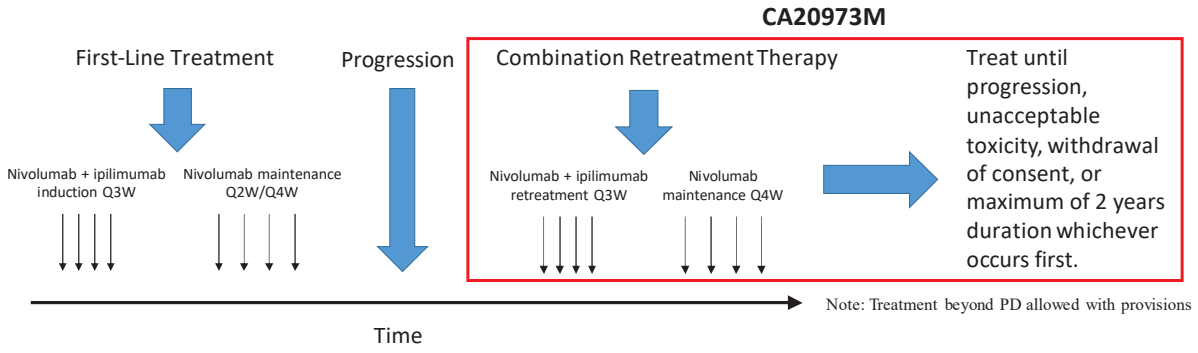
Table 1: Study Treatments for CA20973M

Medication	Potency	IP/Non-IP
Nivolumab	3 mg/kg 480 mg	IP
Ipilimumab	1 mg/kg	IP

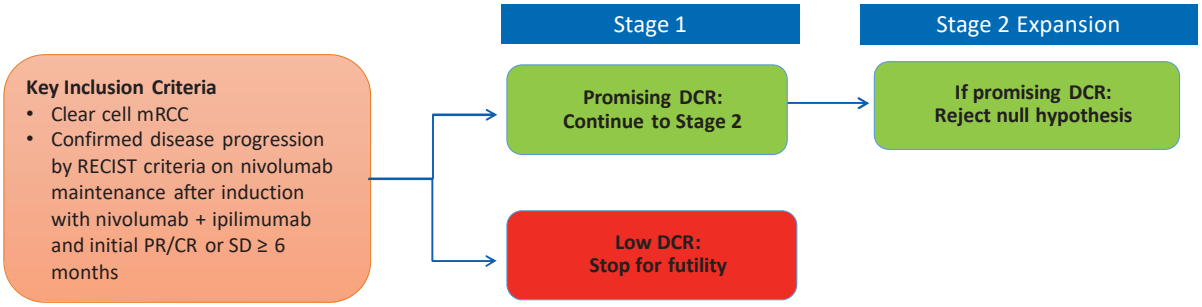
Abbreviation: IP = investigational product

The study design schematic is presented in Figure 1 (red rectangle). The duration of the trial is expected to be approximately 24 months of treatment (Stage 1 + Stage 2) and 36 months of follow-up after the last participant first dosing. A futility analysis will be performed after Stage 1 and the primary analysis will be conducted upon completion of Stage 2.

Figure 1: Study Design Schematic



Simon 2-stage Design



Abbreviations: CR = complete response; DCR = disease control rate; mRCC = metastatic renal cell carcinoma; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1; SD = stable disease

Discontinuation of Participants From Treatment:

Participants will be treated until progression, unacceptable toxicity, or maximum 24 months of study treatment for nivolumab. Once a patient has discontinued from treatment, he or she will continue to be followed for OS for approximately 36 months. All reasonable effort will be made to maintain contact with participants during this follow-up period via phone calls, faxes, or emails.

Steering Committee: No

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA20973M)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Register in IRT system to obtain participant number. The participant must sign the informed consent prior to any study-related assessment being performed.
Inclusion/Exclusion Criteria	X	See Section 6.1 and Section 6.2
Medical History	X	
[redacted]		
Tumor Tissue Samples[a]	X	Archival tumor tissue from the original diagnosis (if available) and tumor tissue obtained at or after progression on nivolumab maintenance (with an associated pathology report) will be collected. FFPE block or 20 unstained slides; a minimum of 15 slides will be acceptable if tumor tissue is limited [redacted].
Safety Assessments		
Complete Physical Examination, Vital Signs, Performance Status	X	Height, weight, KPS (Appendix 7), BP, RR, heart rate, and temperature within 14 days prior to first dose.
Assessment of Signs and Symptoms	X	
Concomitant Medication Use	X	
AE and SAE Assessment	X	SAEs from time of consent (see Section 9.2).
Laboratory Tests		
ECG	X	A single ECG, or triplicate ECGs if abnormal on the first ECG, should be recorded after the participant has been supine for at least 15 minutes.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study treatment.
Additional Tests	X	See Section 9.4.4 for additional details on tests required. To be completed locally at each site. CBC with differential, chemistry panel (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, albumin, Na, K, Cl, Ca [also Ca corrected], Phos, and Mg)

Table 2-1: Screening Procedural Outline (CA20973M)

Procedure	Screening Visit	Notes
		Thyroid panel (includes TSH with free T3 and free T4) Hepatitis B/C (HBVsAg, HCV antibody or HCV RNA) HIV if mandated locally (see Appendix 8) Urinalysis
Efficacy Assessment		
Body Imaging	X	Contrast-enhanced CT of the chest and CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 30 days prior to the date of first dosing (see Section 9.1.1).
Brain Imaging	X	MRI of the brain without and with contrast is required for ALL participants during screening to rule out brain metastases. CT of the brain (without and with contrast) can be performed if MRI is contraindicated (see Section 9.1.1).

[a] Tumor tissues will be collected at screening from original diagnostic archival samples (if available) and after progression on nivolumab maintenance. If samples within ≤ 12 months prior to enrollment are not available, please contact the BMS medical monitor.

Abbreviations: ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; FFPE = Formalin-fixed paraffin-embedded; HBVsAg = hepatitis B virus antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; [redacted] IRT = interactive response technology; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; RNA = ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; T3 = thyroxine; T4 = triiodothyronine; TBili = total bilirubin; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

Table 2-2: On-treatment Procedural Outline Cycles 1 through 4 (CA20973M)

Procedure[a]	Cycle 1 through Cycle 4 (Cycle = 3 weeks) Dosing Q3W for 4 Doses				Notes
	Day 1 Cycle 1	Day 1 Cycle 2	Day 1 Cycle 3	Day 1 Cycle 4	
Safety Assessments					
Targeted Physical Examination, Vital Signs, Performance Status	X	X	X	X	Within 72 hours prior to dosing, weight, BP, RR, heart rate, temperature, and KPS (Appendix 7) to be performed.
Assessment of Signs and Symptoms	X	X	X	X	
AE and SAE Assessment	Continuously				Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All AEs and SAEs will be documented for a minimum of 100 days after last dose (Appendix 3).
Concomitant Medication Use	X	X	X	X	
Laboratory Tests					
Pregnancy Test (WOCBP only)	X	X	X	X	Serum or urine test within 24 hours prior to administration of study drug.
Additional Tests	X	X	X	X	See Section 9.4.4 for additional details on tests required. Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to the first dose unless repeat of tests for eligibility prior to C1D1 dosing is clinically indicated. After C1D1, within 72 hours prior to re-dosing to include: • CBC with differential, chemistry panel at every cycle (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, Na, K, Cl, Ca, Phos, and Mg) • Thyroid panel (includes TSH with reflexive free T3 and free T4) at every cycle
[redacted]					

Table 2-2: On-treatment Procedural Outline Cycles 1 through 4 (CA20973M)

Procedure[a]	Cycle 1 through Cycle 4 (Cycle = 3 weeks) Dosing Q3W for 4 Doses				Notes
	Day 1 Cycle 1	Day 1 Cycle 2	Day 1 Cycle 3	Day 1 Cycle 4	
Efficacy Assessments					
Body Imaging				X	Contrast-enhanced CT of the chest and CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should be performed on Week 12 (± 7 days) following date of first dosing. See Section 9.1.1 for further details.
Brain Imaging					Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner, if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Study Treatment					
Administer nivolumab and ipilimumab	X	X	X	X	Nivolumab is to be administered first (see Section 7.1)

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CT = computed tomography; D = day; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; Q3W = every 3 weeks; RR = respiratory rate; SAE = serious adverse event; T3 = thyroxine; T4 = triiodothyronine; TBili = 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.

Table 2-3: On-treatment Procedural Outline Cycle 5 and Beyond (CA20973M)

Procedure [a]	Cycle 5 and Beyond up to 24 Months of Treatment (Cycle = 4 Weeks)	Notes
	Day 1	
Safety Assessments		
Targeted Physical Examination, Vital Signs, Performance Status	X	Within 72 hours prior to dosing, weight, BP, heart rate, RR, temperature, KPS (Appendix 7), and Performance Status assessment to be performed.
Assessment of Signs and Symptoms	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All AEs and SAEs will be documented for a minimum of 100 days after last dose (Appendix 3).
AE and SAE Assessment	Continuously	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All AEs and SAEs will be documented for a minimum of 100 days after last dose (Appendix 3).
Concomitant Medication Use	X	
Laboratory Tests		
Pregnancy Test (WOCBP only)	X	Serum or urine test within 24 hours prior to administration of study drug.
Additional Tests	X	See Section 9.4.4 for additional details on tests required. Within 72 hours prior to dosing to include: • CBC with differential, chemistry panel at every cycle (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN or serum urea, glucose, Na, K, Cl, Ca, P, and Mg) • Thyroid panel (includes TSH with reflexive free T3 and free T4) at every cycle
[redacted]		

Table 2-3: On-treatment Procedural Outline Cycle 5 and Beyond (CA20973M)

Procedure [a]	Cycle 5 and Beyond up to 24 Months of Treatment (Cycle = 4 Weeks)	Notes
	Day 1	
Efficacy Assessments		
Body Imaging		Subsequent to Week 12, imaging should occur every 8 weeks (± 7 days) until Week 60, then every 12 weeks (± 7 days) until initiation of another anti-cancer treatment, withdrawal of consent, or death, whichever occurs first. See Section 9.1.1 for further details.
Brain Imaging		Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner, if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Study treatment		
Administer nivolumab monotherapy	X	Subsequent doses may be administered within 3 days after the scheduled date if necessary. See Section 7.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CT = computed tomography; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; RR = respiratory rate; SAE = serious adverse event; T3 = thyroxine; T4 = triiodothyronine; TBili = 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.

Table 2-4: Follow-up Procedural Outline (CA20973M)

Procedure	Follow-up Assessments All Participants		Notes
	Follow-Up[a] Visits 1 and 2	Survival[b] Follow-up	
Safety Assessments			
Targeted Physical Examination, Vital Signs, Performance Status	X	--	Weight, BP, heart rate, RR, temperature, and KPS (Appendix 7).
Assessment of Signs and Symptoms	X	--	
AE and SAE Assessment	X	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All AEs and SAEs will be documented for a minimum of 100 days after last dose. (Appendix 3).
Concomitant Medication Use	X	--	
Laboratory Tests			
Pregnancy Test (WOCBP only)	X	--	Serum or urine
Additional Tests	X	--	See Section 9.4.4 for additional details on tests required. CBC with differential, chemistry panel (includes AST, ALT, TBili, ALP, LDH, creatinine, BUN, glucose, Na, K, Cl, Ca, Phos, Mg) Thyroid panel (includes TSH with reflexive free T3 and free T4)
Efficacy Assessments			
Body Imaging	Imaging should occur at every 8 weeks (± 7 days) until Week 60, then every 12 weeks (± 7 days) until initiation of another anti-cancer treatment, withdrawal of consent, or death, whichever occurs first (see Section 9.1.1).		
Brain Imaging	Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks), or sooner, if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.		

Table 2-4: Follow-up Procedural Outline (CA20973M)

Procedure	Follow-up Assessments All Participants		Notes
	Follow-Up[a] Visits 1 and 2	Survival[b] Follow-up	
Survival Status			
Participant Status	X	X	During safety follow-up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent therapy (see Section 8.1.2).

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BMS = Bristol-Myers Squibb; BUN = blood urea nitrogen; CT = computed tomography; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; RR = respiratory rate; SAE = serious adverse event; T3 = thyroxine; T4 = triiodothyronine; TBili = total bilirubin; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

[a] Follow-up visits occur as follows: Follow-up Visit 1 = 30 days (± 7 days) from the last dose or coincide with the date of discontinuation (± 7 days) if date of discontinuation is > 42 days after last dose. Follow-up Visit 2 = 100 days (± 7 days) from last dose of study treatment. Participants must be followed for at least 100 days after last dose of study treatment. Both follow-up visits should be conducted in person.

[b] Survival follow-up visits may be conducted in clinic or by phone. Survival visits: first Survival Follow-up Visit 3 months (± 14 Days) after Follow-up Visit 2, and subsequent survival follow-up visits every 3 months (± 14 days) for approximately 36 months. BMS may request that survival data be collected on all treated participants outside of the 3-month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

3 INTRODUCTION

3.1 Study Rationale

CA209214 was a Phase 3 study of nivolumab in combination of ipilimumab compared with sunitinib in previously untreated patients with locally advanced renal cell carcinoma (RCC) or metastatic renal cell carcinoma (mRCC). The study has demonstrated a favorable benefit/risk profile for the combination of nivolumab and ipilimumab over current standard of care sunitinib in International Metastatic RCC Database Consortium (IMDC) intermediate/poor risk patients as shown by the unprecedented overall survival (OS) benefit in this population. It also showed superior objective response rate (ORR), higher rate of complete response (CR) as well as a clinically meaningful increase in progression-free survival (PFS) compared to sunitinib. While the combination has differential toxicities compared to sunitinib due to different mechanism of action, it has a manageable safety profile and is well tolerated compared to sunitinib.

In patients who achieve initial tumor control (whether CR, partial response [PR], or stable disease [SD]) on the combination but then progress while on nivolumab maintenance, there is good biological rationale for ipilimumab rechallenge (defined as reintroduction of treatment upon disease progression). Indeed, an equilibrium between tumor growth and immunological response is required in order to prevent disease progression. Selective pressure might drive immunoediting and immune escape, resulting in loss of primary tumor response and/or novel antigen repertoire to emerge on new legions. By rechallenging with ipilimumab, the T-cell pool will expand and reactivate the primed immune system to recognize and respond to any remaining original tumor cells or new tumor clones that may have appeared during the tumor escape phase.

In melanoma, clinical data from early studies (MDX010-20, CA184025, CA184243) as well as real-world evidence have provided evidence of the activity of ipilimumab rechallenge for patients who had an initial response or SD with ipilimumab and then progressed, as well as data on the combination of ipilimumab and nivolumab for patients who progressed on anti-programmed cell death protein 1 (PD-1). In mRCC, while recent retrospective studies suggest that the combination nivolumab and ipilimumab can be used as salvage therapy in immuno-oncology (I-O) refractory patients[1], no data exist regarding the retreatment with ipilimumab for patients who show signs of progressive disease on nivolumab maintenance therapy after initial nivolumab and ipilimumab induction.

This study aims to determine if stimulation of an immune response by reintroducing ipilimumab and nivolumab could regain tumor control, as measured by primary endpoint of disease control rate (DCR), with OS, PFS, ORR, and safety as key secondary endpoints. [redacted]

3.1.1 Research Hypothesis

Retreatment with ipilimumab in combination with nivolumab in patients progressing on nivolumab maintenance therapy after ipilimumab and nivolumab induction, will result in improved clinical benefits based on DCR (defined as the percentage of patients who had SD for at least 6 months from first treatment dose, CR, or PR) in patients with mRCC.

3.2 Background

3.2.1 Cancer Immunotherapy

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.[2,3,4] 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.[5] Collectively, these signals govern the balance between T-cell activation and tolerance.

3.2.2 Nivolumab Mechanism of Action

PD-1 (cluster of differentiation [CD]279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), inducible co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[6] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: programmed cell death protein ligand-1 (PD-L1) (B7-H1/CD274) and programmed cell death protein ligand-2 (PD-L2) (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of a protein tyrosine phosphatase SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.

In vitro, nivolumab (Bristol-Myers Squibb [BMS]-936558), a fully human, immunoglobulin (Ig)G4 (kappa [κ]) isotype, monoclonal antibody (mAB) binds to PD-1 with high affinity (EC50 0.39 nM to 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 interferon gamma (IFN-γ) release in the mixed lymphocyte reaction that further increases upon addition of ipilimumab, providing in vitro evidence for synergistic activity of the combination.[7] Using a cytomegalovirus (CMV) stimulation assay with human peripheral blood mononuclear cells, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by

a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[8]

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.[9] 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 antigen-presenting cells, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

3.2.4 Preclinical Summary of Nivolumab Combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve anti-tumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased anti-tumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor-infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[10]

A 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver, and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

3.2.5 Summary of Ipilimumab Rechallenge Studies

Ipilimumab rechallenge in participants progressing after initial immunotherapy treatment has been studied in several BMS-led trials. In the Phase 3 advanced melanoma study MDX010-20, optional retreatment was planned in the study protocol so patients who initially responded to ipilimumab treatment but later progressed were eligible for retreatment with their original randomized regimen. A subanalysis was performed on 38 patients retreated at progression with ipilimumab + gp100 or ipilimumab + placebo after initial clinical benefit (CR, PR, SD) lasting ≥ 6 months from

baseline and an acceptable safety profile during the initial treatment.[11] Best overall response rates (CR plus PR) for 31 retreatment-eligible patients in the ipilimumab + gp100 and ipilimumab + placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively, and DCRs were 65.2% and 75.0%, respectively. Thus, duration of response (DOR) and/or SD were achieved in participants who received retreatment upon initial progression of disease (PD), even after up to 2.5 years between last dose of ipilimumab and additional retreatment courses. Some patients achieved better best overall response (BOR) after retreatment than initial induction. Safety profile of retreatment showed no new types of toxicities, with consistent with safety profile of induction, and most events were of mild-to-moderate severity. Induction toxicity did not predispose to retreatment toxicity.

Study CA184025 was a Phase 2 rollover study of patients treated on prior Phase 2 studies (CA184004, CA184007, CA184008, CA184022, MDX010-08, and MDX010-15) with the primary objective of evaluating the safety of extended treatment with ipilimumab in patients with metastatic melanoma.[12] Of the 122 patients rechallenged with ipilimumab, 7 patients had a CR and 21 patients had a PR by modified World Health Organization criteria for a BOR of 23%. An additional 31 patients had SD; therefore, the DCR upon retreatment was 48%. In this patient population, retreatment with ipilimumab at 10 mg/kg was generally well tolerated and the safety profile was similar to that during induction dosing in the parent studies, with no new safety signals identified. Tolerability to prior ipilimumab at 10 mg/kg does not preclude the development of Grade 3 or 4 immune-related adverse events (irAEs) during retreatment.

Ipilimumab retreatment in patients with pretreated advanced melanoma was also assessed among patients participating in an expanded access program in Italy.[13] Patients who achieved disease control during induction therapy were retreated with ipilimumab upon progression, provided they had not experienced toxicity that precluded further dosing. Of 855 patients treated with ipilimumab, 51 (6%) patients received retreatment upon disease progression. Data from this study showed a retreatment response rate of about 12% and DCR of 55% after ipilimumab rechallenge, with 42% of patients alive 2 years after beginning of induction therapy (33% after start of retreatment) and median OS of 21 months (12 months after start of retreatment). No new types of toxicities occurred during retreatment and most events were of mild-to-moderate severity and resolving within a median of 4 days, with 22% of patients having a treatment-related adverse event (AE) of any grade during retreatment.

In mRCC, no data currently exist on retreatment or rechallenge with ipilimumab. However, a recent retrospective study looked at the activity of salvage nivolumab and ipilimumab combination in 30 patients who have progressed on a variety of prior immunotherapies.[1] The median number of prior therapies was 3, and prior I-O therapies included anti-PD-L1 monotherapy (17 patients [57%]), I-O/anti-vascular endothelial growth factor (VEGF) combination (5 patients [17%]), and nivolumab and ipilimumab combination (1 patient [3%]). The overall ORR on salvage nivolumab and ipilimumab was 23%, and DCR was 36%. Eleven patients (37%) developed any grade irAEs and 2 patients (6%) developed Grade ≥ 3 irAEs.

3.2.6 Indication Background

3.2.6.1 Renal Cell Carcinoma: Background and Standard Treatments

Globally, more than 330,000 cases of RCC are diagnosed annually, with approximately a third of the patients succumbing to their disease. RCC accounts for about 3% of all cancers in the United States (US) where there are approximately 65,000 new cases and almost 15,000 deaths from RCC each year.[14] In the European Union, there were approximately 84,000 cases of RCC and 35,000 deaths in 2012.[15] Metastatic disease is found in 30% of participants at diagnosis. Close to 90% to 95% of metastatic disease has a clear-cell histology. RCC is approximately 50% more common in men compared with women.[16] RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age.

Multiple scoring systems are available to characterize prognosis in treatment-naive RCC. Two of the most commonly used are the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system and the IMDC prognostic scoring system.[17,18] Each of these systems categorizes patients as favorable, intermediate, or poor risk based on how many adverse prognostic factors are present (0: favorable risk, 1 to 2: intermediate risk, 3 or more: poor risk). The 6 parameters of importance for IMDC prognostic score classification are Karnofsky Performance Status (KPS), time from diagnosis to treatment, hemoglobin value, corrected calcium concentration, absolute neutrophil count, and platelet count [redacted]. The 5 parameters included in the MSKCC prognostic score are KPS, nephrectomy status, hemoglobin value, lactate dehydrogenase (LDH), and corrected calcium concentration. Time from diagnosis to treatment is often used in place of nephrectomy status. With each system, the total number of adverse prognostic factors present has been shown to correlate with OS. Approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group (median OS: ~ 9 months). In an analysis of 1,028 patients scored using the IMDC system, median OS for favorable-, intermediate-, and poor-risk patients is 43.2 months, 22.5 months, and 7.8 months, respectively.[19]

Until recently, the cytokines interleukin (IL)-2 and interferon were the only active treatments for advanced RCC or mRCC. However, due to each of these agents' limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of mRCC. There are several agents for the treatment of RCC that target angiogenesis (ie, the VEGF receptor tyrosine kinase inhibitors (TKIs), sorafenib, sunitinib, pazopanib, cabozantinib, and axitinib; and the VEGF-binding mAB, bevacizumab) and 2 that target the mammalian target of rapamycin (mTOR) pathway (ie, everolimus and temsirolimus).

More recently, immunotherapeutic approaches have demonstrated clinical efficacy in RCC with a survival advantage. Nivolumab monotherapy has been approved in multiple countries around the globe for the treatment of patients with mRCC previously treated with anti-angiogenic agents based on the results from CheckMate-025 (CA209025; NCT01668784). Furthermore, combination therapy with nivolumab and ipilimumab has demonstrated superior efficacy over sunitinib in intermediate- and poor-risk patients with previously untreated advanced RCC leading to Food and Drug Administration (FDA) approval of that regimen in the US and other regions.

3.2.6.2 Nivolumab in Renal Cell Carcinoma

Nivolumab monotherapy has been studied in participants with RCC in several BMS sponsored studies, with the largest amount of data coming 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).[20] 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 every 3 weeks (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, 2, 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, 2, and 10 mg/kg, respectively. Related Grade 3 events in at least 2 patients across dose levels included nausea, aspartate aminotransferase (AST)/alanine aminotransferase (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 of 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 versus 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% versus 88%; Grade 3 to Grade 4, 19% versus 37%, respectively) and drug-related AEs leading to discontinuation (all grades, 8% versus 13%, respectively) in the nivolumab group. These results were the basis for regulatory approval of nivolumab monotherapy in advanced RCC.

3.2.6.3 Ipilimumab in Renal Cell Carcinoma

Ipilimumab monotherapy for the treatment of mRCC was studied in the Phase 2 clinical trial MDX010-11.[21] 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 SD or PR or CR were allowed additional treatment. In group 3-1 (n = 21), 1 participant (5%) had a PR.[22] 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 and 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).[21] 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). There were 6 participants (15%) with Grade 4 AEs in group 3-3. 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.

3.2.6.4 Nivolumab Combined with Ipilimumab in Renal Cell Carcinoma

The combination of nivolumab with ipilimumab was studied in the Phase 1 study CA209016.[23] Participants with mRCC (favorable/intermediate MSKCC score; KPS ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg (N3) combined with ipilimumab 1 mg/kg (I1 [arm N3 + I1]) or nivolumab 1 mg/kg (N1) combined with ipilimumab 3 mg/kg (I3 [arm N1 + I3]) intravenously once Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; the secondary objective was to assess anti-tumor activity. Forty-four participants were randomized to N3 + I1 (n = 21) and N1 + I3 (n = 23). Most patients (n = 34; 77%) had prior systemic therapy (N3 + I1: 16 patients; N1 + I3: 18 patients). The confirmed ORR was 43% (N3 + I1) and 48% (N1 + I3). DOR was 4.1+ to 42.1+ weeks (7 of 9 responses ongoing) in N3 + I1, and 12.1+ to 35.1+ weeks (9 of 11 responses ongoing) in N1 + I3. Best response of disease standard deviation was seen in 5 patients (24%; N3 + I1) and 8 patients (35%; N1 + I3). Median PFS was 36.6 weeks (N3 + I1) and 38.3 weeks (N1 + I3); these data are still immature, with 11 of 21 events reported for N3 + I1 and 10 of 23 events reported for N1 + I3.

The safety of nivolumab combined with ipilimumab was assessed in CA209016. Treatment-related AEs were seen in 39 patients (89%), including 16 (76.2%) in N3 + I1 and 23 (100%) in N1 + I3. Across the N3 + I1 and N1 + I3 arms, the most common (≥ 20%) treatment-related AEs of any Grade were fatigue (61%), diarrhea (32%), nausea (30%), rash (27%), pruritus (25%), ALT increased (23%), AST increased (20%), hypothyroidism (20%), and lipase increased (20%). Grade 3 or Grade 4 related AEs occurred in 19 patients (29%), including 6 (29%) at N3 + I1 and 14 (61%) at N1 + I3. The most common (≥ 5%) drug-related Grade 3 or Grade 4 events were lipase increased (21%), ALT increased (14%), AST increased (7%), diarrhea (9%), fatigue (5%), amylase

increased (5%), colitis (5%), and lymphocyte count decreased (5%). No Grade 3 or Grade 4 pneumonitis was seen. No treatment-related deaths were reported.

In summary, a similar robust level of clinical activity was observed with N3 + I1 and N1 + I3, but the N3 + I1 arm exhibited a more favorable safety profile.

Study CA209214 is a Phase 3, randomized, open-label study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W versus sunitinib monotherapy using the approved dose and schedule (50 mg orally once daily for 4 weeks followed by 2 weeks off, every cycle) in adult participants with previously untreated advanced RCC. The combination therapy with nivolumab and ipilimumab has demonstrated superior efficacy over standard of care sunitinib in intermediate- and poor-risk patients with previously untreated advanced RCC and is now established as the new standard of care in this setting with regulatory approvals in the US, Canada, Japan, and Switzerland. In the Phase 3 trial CheckMate 214, a total of 1,096 participants were randomized, including 847 participants with IMDC intermediate and poor risks (425 participants in the nivolumab combined with ipilimumab group and 422 participants in the sunitinib group). The median OS was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (HR for death, 0.63; P < 0.0001) (Table 3.2.6.4-1). The ORR was 42% versus 27% (P < 0.0001), with a CR rate of 9.4% versus 1.2%. Independent Regulatory Review Commission-assessed PFS in intermediate/poor-risk participants also favored nivolumab combined with ipilimumab over sunitinib, demonstrating a 3.2-month improvement in median PFS (11.56 months versus 8.38 months). The PFS curves separated after a delay of approximately 6 months from randomization, resulting in an HR of 0.82 that did not meet the prespecified alpha boundary of 0.009 for statistical significance.

Table 3.2.6.4-1: Summary of Efficacy Results in CA209214

	Intermediate/Poor-risk Patients		**All Randomized (Any Risk) Patients**	
	Nivolumab + Ipilimumab (N = 425)	**Sunitinib (N = 422)**	**Nivolumab + Ipilimumab (N = 550)**	**Sunitinib (N = 546)**
OS				
N events (%)	140 (32.9)	188 (44.5)	161 (29.3)	204 (37.4)
Median OS (months)[a]	NA	25.95	NA	32.92
Exact 95% CI	(28.16, NA)	(22.08, NA)	-	(NA, NA)
HR (99.8% CI)[b]	0.63 (0.44, 0.89)		0.68 (0.49, 0.95)	
p-value [c]	<0.0001		0.0003	

Table 3.2.6.4-1: Summary of Efficacy Results in CA209214

	Intermediate/Poor-risk Patients		All Randomized (Any Risk) Patients	
	Nivolumab + Ipilimumab (N = 425)	Sunitinib (N = 422)	Nivolumab + Ipilimumab (N = 550)	Sunitinib (N = 546)
IRRC-assessed ORR (CR+PR)[d]	***Co-primary Objective***		***Secondary Objective***	
N responders (%)	177 (41.6)	112 (26.5)	213 (38.7)	176 (32.2)
Exact 95% CI	36.9, 46.5	22.4, 31.0	34.6, 42.9	28.3, 36.3
Difference in ORR (95% CI)[e,f]	16.0 (9.8, 22.2)		7.2 (1.8, 12.7)	
p-value[g]	<0.0001		0.0191	
BOR				
CR	40 (9.4)	5 (1.2)	54 (9.8)	12 (2.2)
PR	137 (32.2)	107 (25.4)	159 (28.9)	164 (30.0)
SD	133 (31.3)	188 (44.5)	199 (36.2)	232 (42.5)
PD	83 (19.5)	72 (17.1)	99 (18.0)	78 (14.3)
UTD	31 (7.3)	50 (11.8)	38 (6.9)	59 (10.8)
DOR				
Median (95% CI), months[a]	NA (21.82, NA)	18.17 (14.82, NA)	NA (21.82, NA)	20.96 (18.17, NA)
Min, Max[h]	1.4+, 25.5+	1.3+, 23.6+	1.4+, 27.7+	1.3+, 26.3+
IRRC-assessed PFS	***Co-primary Objective***		***Secondary Objective***	
N events (%)	228 (53.6)	228 (54.0)	296 (53.8)	271 (49.6)
Median PFS (months)[a]	11.56	8.38	12.42	12.32
Exact 95% CI	(8.71, 15.51)	(7.03, 10.81)	(9.89, 16.53)	(9.79, 15.24)
HR (99.1% CI)[b]	0.82 (0.64, 1.05)		0.98 (0.79, 1.23)	
p-value[c]	0.0331		0.8498	

Source: CA209214 Final CSR[24], Table 7.1-1

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; IMDC = International Metastatic RCC Database Consortium; IRRC = Independent Regulatory Review Commission; IVRS = interactive voice response system; Max = maximum; Min = minimum; N = number of patients; NA = not applicable; ORR = objective response rate; OS = overall survival; PD = progression of disease; PFS = progression-free survival; PR = partial response; ROW = rest of the world; SD = stable disease; US = United States; UTD = unable to determine

[a] Median computed using Kaplan-Meier method.

[b] Stratified Cox proportional hazard model. HR is nivolumab combined with ipilimumab over sunitinib.

[c] Log-rank Test stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (US, Canada/W Europe/N Europe, ROW) as entered into the IVRS.

[d] CI based on the Clopper and Pearson method.

[e] Strata adjusted difference in ORR (nivolumab + ipilimumab – sunitinib) based on DerSimonian and Laird method.

[f] Stratified by IMDC prognostic risk score (0, 1-2, 3-6) and region (US, Canada/western Europe/northern Europe, Rest of World) as entered into the IVRS.

[g] Two-sided p-value from DerSimonian and Laird Test.

[h] Symbol "+" indicates a censored value.

Significant benefit was also observed with nivolumab combined with ipilimumab regardless of PD-L1 tumor expression although the benefit was somewhat higher in the PD-L1-positive population. In CA209214, the safety of the combination nivolumab combined with ipilimumab is acceptable with a tolerable and manageable safety profile (Table 3.2.6.4-2). The majority of select AEs and immune-mediated adverse events (IMAEs) were low-grade and manageable using the recommended treatment guidelines for early work-up and intervention. The overall safety profile observed in the nivolumab combined with ipilimumab group was consistent with the known and well-characterized safety profile of nivolumab monotherapy, as well as the nivolumab and ipilimumab combination, and was similar to the profile observed across other tumor types in terms of type, frequency, and severity of AEs observed. There were no new safety concerns identified.

Table 3.2.6.4-2: Summary of Safety Results - All Treated Patients in CA209214

	Number (%) Patients			
	Nivolumab + Ipilimumab (N = 547)		Sunitinib (N = 535)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-related AEs	509 (93.1)	250 (45.7)	521 (97.4)	335 (62.6)
Most frequent drug-related AEs (≥ 15% of any grade in either treatment group)				
Fatigue	202 (36.9)	23 (4.2)	264 (49.3)	49 (9.2)
Pruritus	154 (28.2)	3 (0.5)	49 (9.2)	0
Diarrhoea	145 (26.5)	21 (3.8)	278 (52.0)	28 (5.2)
Rash	118 (21.6)	8 (1.5)	67 (12.5)	0
Lipase increased	90 (16.5)	56 (10.2)	58 (10.8)	35 (6.5)
Nausea	109 (19.9)	8 (1.5)	202 (37.8)	6 (1.1)
Hypothyroidism	85 (15.5)	2 (0.4)	134 (25.0)	1 (0.2)
Decreased appetite	75 (13.7)	7 (1.3)	133 (24.9)	5 (0.9)
Asthenia	72 (13.2)	8 (1.5)	91 (17.0)	12 (2.2)
Vomiting	59 (10.8)	4 (0.7)	110 (20.6)	10 (1.9)
Anaemia	34 (6.2)	2 (0.4)	83 (15.5)	24 (4.5)

Table 3.2.6.4-2: Summary of Safety Results - All Treated Patients in CA209214

	Number (%) Patients			
	Nivolumab + Ipilimumab (N = 547)		Sunitinib (N = 535)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Dysgeusia	31 (5.7)	0	179 (33.5)	1 (0.2)
Stomatitis	23 (4.2)	0	149 (27.9)	14 (2.6)
Dyspepsia	15 (2.7)	0	96 (17.9)	0
Mucosal inflammation	13 (2.4)	0	152 (28.4)	14 (2.6)
Hypertension	12 (2.2)	4 (0.7)	216 (40.4)	85 (15.9)
Palmar-plantar erythrodysaesthesia syndrome	5 (0.9)	0	231 (43.2)	49 (9.2)
Thrombocytopenia	2 (0.4)	0	95 (17.8)	25 (4.7)
Drug-related Select AEs, by Category				
Endocrine	178 (32.5)	38 (6.9)	163 (30.5)	1 (0.2)
Gastrointestinal	154 (28.2	27 (4.9)	278 (52.0)	28 (5.2)
Hepatic	101 (18.5)	45 (8.2)	77 (14.4)	20 (3.7)
Pulmonary	34 (6.2)	6 (1.1)	1 (0.2)	0
Renal	48 (8.8)	7 (1.3)	46 (8.6)	6 (1.1)
Skin	267 (48.8)	20 (3.7)	304 (56.8)	53 (9.9)
Hypersensitivity/infusion reactions	22 (4.0)	0	6 (1.1)	2 (0.4)

Source: CA209214 Final CSR[24], Table 8.1-1

Abbreviations: AE = adverse event; CSR = clinical study report; CTC = common terminology criteria; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients.

Notes: MedDRA version 20.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

3.3 Benefit/Risk Assessment

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

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

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

Patients with mRCC have multiple treatment options available to them (see Section 3.2.6.1), but none of the 7 available targeted agents have been able to demonstrate a significant improvement in OS when compared to each other. Median OS remains less than 4 years for treatment-naive patients with the most favorable prognosis and is substantially shorter for patients who possess adverse prognostic factors. Therefore, new therapeutic options with the potential to provide greater survival are needed.

Nivolumab in combination with ipilimumab in the 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. Retreatment with ipilimumab regimen for patients who had initial clinical benefit but who have progressed on nivolumab maintenance is expected to regain tumor control and show a clinical meaningful DCR of with a manageable increase in IMAEs.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To describe the efficacy in terms of DCR of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab	• DCR is defined as the proportion of participants who achieve a confirmed best response of CR, PR, or SD for at least 6 months after first treatment dose per RECIST 1.1 criteria.
Secondary	
• To describe the OS of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• OS is defined as the time from first dose to the date of death from any cause. For participants that are alive, their survival time will be censored at the date of last contact ("last known alive date"). OS will be censored for participants at the date of first dose if they were treated but had no follow-up.
• To evaluate additional efficacy measures in all participants.	• ORR is defined as the proportion of participants who achieve a best response of CR or PR per RECIST 1.1 criteria. • DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression, per RECIST 1.1 criteria, or death due to any cause, whichever occurs first. • PFS is defined as the time between the date of first dose and the first date of documented progression, as per RECIST 1.1 criteria, or death due to any cause, whichever occurs first. • Time to objective response (TTR) is defined as the time between the date of the first dose and the first confirmed documented response (CR or PR) per RECIST 1.1 criteria.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To estimate the incidence of AEs of retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab.	• AE incident rate is defined as the proportion of participants with any grade AEs. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.
[redacted]	

Abbreviations: AE = adverse event; CR = complete response; DCR = disease control rate; DOR = duration of response; [redacted] mRCC = metastatic renal cell carcinoma; ORR = objective response rate; OS = overall survival; [redacted] PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; SD = stable disease; TTR = time to objective response

5 STUDY DESIGN

5.1 Overall Design

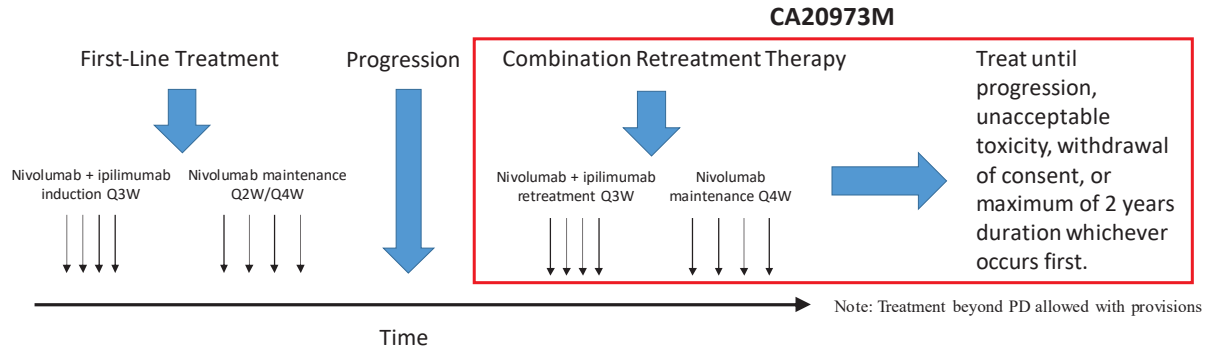
This is a Phase 2, international, multicenter study of rechallenge with ipilimumab 1 mg/kg Q3W combined with nivolumab 3 mg/kg for up to 4 doses followed by nivolumab 480 mg every 4 weeks (Q4W).

- The study will enroll participants previously treated with combination regimen ipilimumab and nivolumab for advanced RCC and mRCC, who had an initial response of CR, PR, or SD for at least 6 months, and who had a confirmed progression on nivolumab maintenance. The number of enrolled participants with SD ≥ 6 months will be capped at 50%. Evaluable tumor tissue, recently acquired after confirmed progression, must be obtained prior to treatment initiation.
- Participants should not have experienced any prior AE that meets the criteria for treatment discontinuation as described in Section 7.4.4, with the exception of patients with prior history of adrenal insufficiency that are under control with hormone replacement.
- The study treatment will continue until participants experience disease progression per RECIST 1.1, unacceptable toxicity, or a maximum of 24 months of study treatment with nivolumab. There is a maximum of 4 doses of ipilimumab.

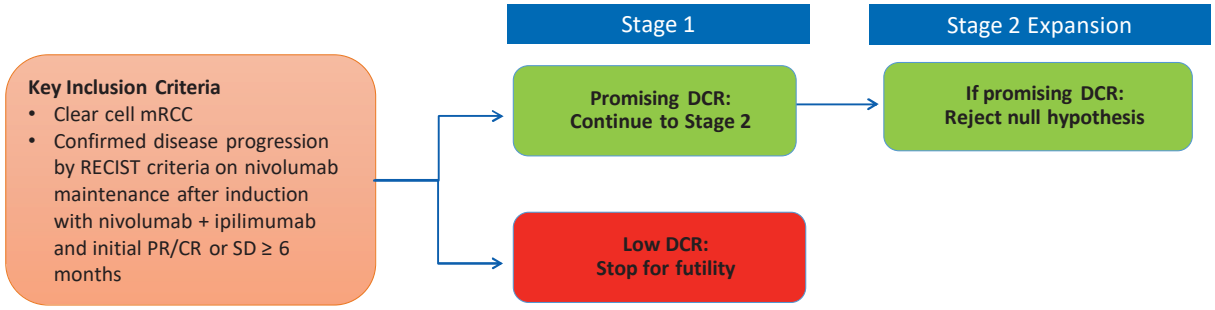
- For drug-related toxicities, dosing of both drugs can be delayed and resumed after resolution per protocol-specified criteria (Sections 7.4.2 and 7.4.3, respectively). No dose increases or reductions are allowed for either drug. Management algorithms of the drug-related toxicities, including the use of corticosteroids and other immunomodulating agents, are provided in Appendix 5.
- During the combination phase (Cycles 1 through 4), participants unable to resume nivolumab and ipilimumab for drug-related toxicities will be permitted to proceed to nivolumab monotherapy maintenance (Section 7.4.4).
- Participants should have baseline computed tomography (CT)/MRI scan results showing measurable disease lesion(s) per RECIST 1.1 and first postbaseline tumor assessment at Week 12 followed by subsequent tumor assessments every 8 weeks in the first 60 weeks, and every 12 weeks thereafter (Section 9.1.1 for more details). The tumor assessment schedule should continue until initiation of another anti-cancer treatment. Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study.
- AE and serious adverse event (SAE) data should be collected throughout the study until 100 days after the last dose. Safety laboratory tests, including complete blood count and chemistry, will be obtained at each schedule visit and unscheduled visit as indicated. [redacted]
- Participants who discontinue the study treatment will be followed for safety at 30 days (± 7 days, Follow-up Visit 1) and 100 days (± 7 days, Follow-up Visit 2) of the last dose, thereafter for survival. Tumor assessments will continue in follow-up period per schedule until initiation of another anti-cancer treatment.

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

Figure 5.1-1: Study Design Schematic



Simon Two-stage Design



Abbreviations: CR = complete response; DCR = disease control rate; mRCC = metastatic renal cell carcinoma; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1; SD = stable disease

This study will consist of 3 phases: screening, treatment, and follow-up.

Screening Stage

Screening begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). Sufficient, recent tumor tissue (obtained at or after progression on initial nivolumab monotherapy) from a metastatic tumor lesion or from a primary tumor lesion that has not been previously irradiated (formalin-fixed paraffin-embedded [FFPE] block or 20 unstained slides; a minimum of 15 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) will be submitted to the designated laboratory. Tumor tissue may be obtained within ≤ 12 months prior to enrollment, preferably within 3 months or during the screening period.

Participants will be assessed for complete study eligibility prior to first dose as specified in Table 2-1. The maximum amount of time between confirmation of study eligibility and the date of first dose is 7 days.

The Screening stage ends with either confirmation of full eligibility or with the confirmation that the participant is a screen failure. This study permits the re-enrollment of a participant who discontinued the study as a pre-treatment failure prior to treatment. If re-enrolled, the participant

must be reconsented. A new participant identification number will be assigned by IRT at the time of re-enrollment.

Treatment Stage

The treatment stage begins after confirmation of full eligibility and consists of:

- Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for up to 4 doses followed by nivolumab 480 mg flat dose IV Q4W
  - Treatment is to be continued until disease progression or unacceptable toxicity. Nivolumab treatment may be administered for a maximum of 24 months from the date of the first dose in Cycle 1.
- The duration for the first 4 cycles is 3 weeks each. The duration of Cycle 5 and beyond is 4 weeks each, with up to 24 months of treatment.

See Table 7.1-1 for the dosing schedule and Section 5.5 for dose and timing justification. Study treatments may be delayed for reasons such as toxicity (see Section 7.4.2). Treatment may be continued beyond investigator-assessed progression if the investigator confirms that the participant meets the criteria specified in Section 8.1.1. A negative pregnancy test should be documented within 24 hours prior to the initial dose of the investigational product (IP) and then performed prior to administration of study drug or as part of follow-up assessment as described in Section 2. On-study laboratory assessments should be drawn within 72 hours prior to dosing and will be assessed at the local laboratory.

[redacted] AE assessments should be documented at each clinic visit.

The Treatment stage ends when the participant is discontinued from study therapy or completes treatment.

Follow-up Stage

The Follow-up stage begins when the decision to discontinue a participant from study therapy is made or the participant completes treatment (no further study treatment). Participants must be followed for at least 100 days (± 7 days) after the last dose of study treatment.

- Follow-up Visit 1 should occur 30 days (± 7 days) from the last dose or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose.
- Follow-up Visit 2 (FU2) occurs approximately 100 days (± 7 days) from the last dose of study treatment.
- Both follow-up visits should be conducted in person.
- AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible.

After FU2, all participants will be followed for OS status every 3 months (± 14 days) for approximately 36 months.

- Survival status can be ascertained in person or by telephone contact.
- If new anti-tumor therapy is initiated for either progression 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 Steering Committee and Other External Committees

Not Applicable

5.2 Number of Participants

Approximately 96 participants will be enrolled in order to obtain 80 response evaluable participants, accounting for approximatively 20% of non-evaluable participants or withdrawal. The number of enrolled participants with SD ≥ 6 months will be capped at 50%.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint (OS) 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 the Study Population

In Study CA209214 with first-line treatment of patients with advanced RCC or mRCC, the clinical benefits of nivolumab combined with ipilimumab were highly significant over sunitinib in the intermediate- and poor-risk groups, indicating (I-O) therapy is most likely to provide benefits to these risk groups. Moreover, data from melanoma studies (see Section 3.2.5) suggests that ipilimumab and nivolumab rechallenge is likely to provide clinical benefit to participants who had an initial disease control (CR, PR, or SD ≥ 6 months).

5.4.2 Rationale for Choice of DCR as Primary Endpoint

In clinical studies, DCR is generally a reliable measure of anti-tumor activity that is not confounded by subsequent therapies. For the present study, the primary endpoint of DCR defined as CR + PR + SD > 6 months was selected based on its clinical relevance in this patient population and as such, its potential to inform medical practice. Given the potential for disease control with immunotherapy and the response rate observed with combined nivolumab and ipilimumab in CA209214, an optimal primary endpoint would capture both objective response and durable SD that is more meaningful than the clinical benefit expected from second-line targeted therapies in this patient population. The DCR as defined for this protocol meets these criteria. Durable SD of 6 months is clinically meaningful in these patients and discriminate between durable SD and slow disease progression. This definition of DCR has been used as primary endpoint to assess the clinical benefit of nivolumab and ipilimumab in melanoma metastatic to the brain.[25]

5.4.4 Rationale for 2-year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[30] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[31]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety

and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 participants with non-small cell lung cancer [NSCLC]), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[32] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29% and 3-year OS rates of 16% to 18% for squamous and non-squamous NSCLC, respectively).[33]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg Q3W) versus docetaxel in participants with previously treated, PD-L1-positive, advanced NSCLC that specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, P = 0.00017) and pembrolizumab 10 mg/kg (HR 0.60, P < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with SD, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[34]

Keynote-006 was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2-year duration of pembrolizumab treatment. One hundred four (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[35]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI, 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[36]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond 2 years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 24 months from the start of study treatment.

5.5 Justification for Dose

5.5.1 Clinical Pharmacology Summary

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

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute IV infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreased over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss was not considered clinically relevant. Nivolumab CL does not decrease over time in patients with completely resected melanoma, as the geometric mean population CL is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The predicted exposure (average concentration [Cavg] and maximum observed concentration [Cmax]) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

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

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

Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated by a PPK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 mL/min/1.73 m^2 to 89 mL/min/1.73 m^2), moderate (eGFR 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2), or severe (eGFR 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2) renal

impairment. No clinically important differences in the CL of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated by PPK analyses in patients with hepatocellular carcinoma and in patients with other tumors with mild hepatic impairment (total bilirubin [TBili] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TBili greater than 1 to 1.5× ULN and any AST) and in patients with hepatocellular carcinoma with moderate hepatic impairment (TBili greater than 1.5 to 3× ULN and any AST). No clinically important differences in the CL of nivolumab were found between patients with mild/moderate hepatic impairment.

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

5.5.2 Justification for Combination Nivolumab and Ipilimumab

In this study, nivolumab 3 mg/kg Q3W will be combined with ipilimumab 1 mg/kg Q3W for up to 4 cycles and then switched to nivolumab 480 mg Q4W during the maintenance phase 3 weeks after the last combination dose. At the first nivolumab 480 mg Q4W dose, ipilimumab concentrations from the combination dose will decline by 2-fold and would approximate ipilimumab concentrations to that of a 0.5-mg/kg Q3W ipilimumab dose. A prior study in advanced melanoma patients demonstrated acceptable safety and tolerability of a combination dosing regimen of nivolumab 6 mg/kg Q4W (body-weight based equivalent of 480 mg Q4W flat dose for an 80-kg subject) in combination with ipilimumab 1 mg/kg Q8W dosed continuously.[37] This combined with prior exposure-response analysis in RCC, which demonstrated that nivolumab exposures when dosed with ipilimumab are not a significant predictor of IMAEs,[38] suggest that no additional washout is warranted before starting the nivolumab 480 mg Q4W maintenance dose.

Data in support of the nivolumab 3 mg/kg Q3W combined with ipilimumab 1 mg/kg Q3W regimen in RCC come from a Phase 2 clinical study (CA209016) and a Phase 3 clinical study (CA209214). Data from CA209016 demonstrated a level of clinical activity, as measured by ORR, for the combination of nivolumab combined with ipilimumab that was substantially greater than that of either nivolumab or ipilimumab monotherapy in mRCC. The dosing regimen including nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg was chosen because it exhibited similar clinical activity to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg with a more favorable safety profile.

In the Phase 3 clinical study (CA209214), the clinical benefit of OS was demonstrated in the intermediate/poor risk population (HR 0.63 [99.8% CI, 0.44 to 0.89])[24] for the N3 Q3W combined with I1 Q3W regimen dosed for 4 cycles followed by N3 Q2W maintenance compared to sunitinib in first-line RCC.

6 STUDY POPULATION

Participants previously treated with combination regimen ipilimumab and nivolumab for advanced RCC and mRCC, who had an initial response of CR, PR or SD for at least 6 months and who had a confirmed progression on nivolumab maintenance.

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 Institutional Review Board (IRB)/Independent Ethics Committee (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) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (American Joint Committee on Cancer Stage IV) RCC

b) Histological confirmation of RCC with a clear-cell component, including participants who may have sarcomatoid features

c) Investigator-assessed, per RECIST 1.1, disease progression on nivolumab maintenance after induction with ipilimumab and nivolumab and PR/CR or SD ≥ 6 months after starting initial induction treatment.

d) Measurable disease by CT or MRI per RECIST 1.1 criteria. Radiated lesions cannot be used as measurable lesions, unless there is clear evidence of progression.

e) KPS of at least 70% or higher.

f) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained at or after progression on initial nivolumab monotherapy maintenance, with an associated pathology report, must be submitted. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is unacceptable for submission. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission [redacted].

3) Age and Reproductive Status

a) Males and females, ages 18 or older.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) 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) Azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study drug being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy and, when applicable, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly (Appendix 4).

6.2 Exclusion Criteria

1) Medical Conditions

a) Any active central nervous system (CNS) metastases

b) Any prior AE that meets the criteria for treatment discontinuation as described in Section 7.4.4, with the exception of patients with prior history of adrenal insufficiency that are under control with hormone replacement.

c) Participants with treated CNS metastases for at least 1 month are eligible as long as they meet the following criteria:

   i) Treated CNS metastases are defined as having no ongoing requirement for corticosteroids for at least 2 weeks (14 days) prior to first dose and no evidence of progression after treatment completed prior to first dose, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or CT). Stable dose of anticonvulsants is allowed. Treatment for CNS metastases may include whole brain radiotherapy, radiosurgery (eg, radiosurgery, gamma knife, linear accelerator, or equivalent) or a combination as deemed appropriate by the treating physician.

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 (eg, celiac disease) are permitted to enroll.

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

f) Uncontrolled adrenal insufficiency

g) Active infection requiring systemic therapy within 14 days prior to the first treatment dose

h) Not applicable per revised protocol 01.

i) Participants with HIV infections are excluded if any of the following applies:
   i) CD4+ T-cell count < 350 cells/μL
   ii) Any AIDS-defining opportunistic infection occurred in the last 12 months
   iii) HIV viral load is ≥ 400 copies/mL
   iv) Antiretroviral therapy has been administered at current doses for less than 4 weeks
   v) The participant is not on antiretroviral therapy

j) Participants with a history of chronic hepatitis B or C are excluded if any of the following applies:
   i) For participants with chronic hepatitis B: The HBV viral load is detectable.
   ii) For participants with chronic hepatitis C: The HCV viral load is detectable.

k) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study treatment.

l) Radiotherapy within 4 weeks except palliative radiation to bone lesions, which requires 2 weeks washout prior to the first dose of study treatment.

m) Prior malignancy (except for mRCC) active within the previous 3 years from screening 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.

n) Presence of any toxicities attributed to prior anticancer therapy, other than alopecia, that have not resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5.0) or baseline before administration of study treatment

o) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis)

p) Women who are breastfeeding

2) Prior/Concomitant Therapy

a) Use of an investigational agent or an investigational device within 28 days before administration of first dose of study treatment

b) Prior treatment with a VEGF-targeted agent except when used as a neoadjuvant or adjuvant therapy with recurrence > 6 months after the last dose of the therapy

c) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to treatment. Refer to Section 7.7.1 for prohibited therapies.

d) Participants who have received a live/attenuated vaccine within 30 days of first treatment.
   i) The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

3) Physical and Laboratory Test Findings

a) White blood cells < 2,000/μL

b) Neutrophils < 1,500/μL

c) Platelets < 100,000/μL
d) Hemoglobin < 9.0 g/dL
e) Serum creatinine > 1.5× ULN, unless calculated creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockroft-Gault formula):

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

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

f) AST/ALT > 3.0× ULN (> 5× ULN if liver metastases are present)
g) TBili > 1.5× ULN (except participants with Gilbert syndrome, who must have a TBili level of < 3.0× ULN)

4) Allergies and Adverse Drug Reaction

a) Known history of allergy or hypersensitivity to study treatment components
b) Known history of severe hypersensitivity reaction to any mAB

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

6.4.1 Retesting During Screening or Lead-in Period

This study permits the re-enrollment of a participant who discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must re-consent.

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

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

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

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

Study treatment includes investigational [medicinal] product (IP/IMP) and consists of the following (Table 7-1):

- Nivolumab Solution for Injection
- Ipilimumab Solution for Injection

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

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-IPs.

Table 7-1: Study Treatments for CA20973M

Product Description / Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558 (Nivolumab) Solution for Injection	10 mg/mL	IP	Open label	Vials	Refer to the label on container and/or Pharmacy Manual.
BMS-734016 (Ipilimumab) Solution for Injection	5 mg/mL	IP	Open label	Vials	Refer to the label on container and/or Pharmacy Manual.

Abbreviations: IMP = investigational medicinal product; IP = investigational product.

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

7.1 Treatments Administered

Treatments should be administered according to Table 7.1-1.

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

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

There will be no dose increases or reductions of nivolumab allowed. Participants may be dosed no less than 19 days from the previous dose during Q3W cycles. For Q4W dosing cycles, participants may be dosed within a ± 3-day window. Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.5.

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

Treatment should be continued until disease progression or unacceptable toxicity, with a maximum nivolumab treatment of 24 months from the first dose in Cycle 1.

Nivolumab injection, 100 mg/10 mL (10 mg/mL) is to be administered as a 30-minute IV infusion through a 0.2-µm to 1.2-µm pore size, low-protein binding in-line filter at the protocol-specified doses.[39,40] It is not to be administered as an IV push or bolus injection. For instructions on storage, preparation, and administration of nivolumab, please refer to the current IB and/or pharmacy manual. Care must be taken to ensure sterility of the prepared solution, as the product does not contain any antimicrobial preservative or bacteriostatic agent.

For instructions on storage, preparation, and administration of ipilimumab, please refer to the current IB and/or pharmacy manual.

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Dosage level(s) and Formulation	Frequency of Administration	Route of Administration
Nivolumab	3 mg/kg 480 mg	Q3W for 4 doses Q4W (maintenance)	IV
Ipilimumab	1 mg/kg	Q3W for 4 doses	IV

Abbreviations: IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks

Note: After 4 doses of study treatment Q3W, participants receive nivolumab monotherapy. Monotherapy begins 3 weeks after their last Q3W dose.

7.2 Method of Treatment Assignment

Not applicable.

7.3 Blinding

This is a non-randomized, open-label study; blinding procedures are not applicable.

7.4 Dosage Modification

I-O agents are associated with AEs that can differ in type, severity, and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. The safety profile of nivolumab and in combination of ipilimumab is described in the IB. Management of drug-related AE includes dose modification and medical interventions, and supportive care should be carefully considered. The recommended management algorithms for IMAE are outlined in Appendix 5 in the following groups: GI, Renal, Pulmonary, Hepatic, Endocrinopathy, Skin, and Neurological. In general, both nivolumab and ipilimumab have similar safety profiles and overlapping IMAEs. The management algorithms and criteria for dose delay, resumption, or discontinuation should be applicable for both drugs. Both drugs should be delayed, resumed, or discontinued when the criteria are met.

7.4.1 Dose Modifications

Dose reductions or dose increases of nivolumab or ipilimumab are not permitted.

7.4.2 Dose Delay Criteria

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 nonskin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or TBili 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, and/or TBili will require dose discontinuation (see Section 7.4.4).
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication

During Cycles 1 to 4, both nivolumab and ipilimumab must be delayed at the same time.

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

7.4.3 Criteria to Resume Treatment

Delayed doses of study treatment should be administered as soon as the participant meets criteria to resume treatment. If a dose has been delayed, the participant should not wait until the next scheduled dosing date.

Participants may resume study treatment when the drug-related AEs resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT, and/or TBili abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, has been completed.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS medical monitor or designee.
- Participants with drug-related endocrinopathies that are adequately controlled with only physiologic hormone replacement may resume treatment.

7.4.4 Criteria for Treatment Discontinuation

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

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

For participants who discontinue study treatment without documented disease progression, tumor and other assessments per protocol-defined schedule should be followed until initiation of another anti-cancer treatment, withdrawal of consent, or death, whichever occurs first.

7.4.4.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for 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 retreatment 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, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or TBili requires discontinuation*
    - Concurrent AST or ALT > 3× ULN and TBili > 2× ULN

  *In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS medical monitor/designee must occur.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or TBili), except for the following events, which 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 AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (eg, corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS medical monitor.
- Any event that leads to delay in dosing lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons, if approved by the BMS medical monitor (or designee)

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS medical monitor (or designee) must be consulted. Tumor and other assessments should continue per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q3W during induction, Q4W during maintenance, or more frequently if clinically indicated during such dosing delays.

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.

7.4.4.2 Ipilimumab Dose Discontinuation

Ipilimumab treatment should be permanently discontinued for 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 retreatment 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, myocarditis, 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT, or TBili requires discontinuation*
      - Concurrent AST or ALT > 3× ULN and TBili > 2× ULN

  *In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS medical monitor/designee must occur.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, and TBili), except for the following events, which 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 AEs, such as hyper- or hypothyroidism or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (eg, corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS medical monitor.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS medical monitor (or designee) must be consulted. Tumor and other assessments should continue per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q3W during induction, Q4W during maintenance, or more frequently if clinically indicated during such dosing delays.

Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued ipilimumab dosing.

7.4.5 Treatment of Infusion-related Reactions

Because nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. 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 BMS medical monitor or designee and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE [version 5.0] guidelines.

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

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

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1,000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms - moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, and 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 paracetamol (acetaminophen) 325 mg to 1,000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1,000 mg should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows. Recommend bronchodilators, epinephrine 0.2 mg to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.5 Preparation/Handling/Storage/Accountability

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

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

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

IP documentation (whether supplied by BMS or not) must be maintained and should include 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 and administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the appropriate IB and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

Not applicable because treatment is injected and/or infused.

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 antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment is permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, or rubella) during treatment and until 100 days post last dose

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 7.4.5 for premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

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 first dose 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.

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted after at least 1 postbaseline tumor assessment if it is clinically indicated.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and, if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, eGFR < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image acquisition manual.

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

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 > 10 mg daily prednisone equivalent are permitted. A brief (< 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

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

Concomitant medications are recorded at baseline and throughout the treatment phase of the study 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 that are different from the study treatment must be documented in the concomitant therapy section of the CRF.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment for the maximum treatment duration as specified in Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

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

If a participant meets the criteria for discontinuation and the investigator is unable to determine whether the event is related to both or 1 study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality, or intercurrent illness that, 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Criteria listed in Section 7.4.4.
- Disease progression of RCC or occurrence of a secondary malignancy that requires systemic therapy for treatment

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed

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

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 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[10]

Participants will be permitted to continue study treatment beyond initial RECIST 1.1-defined (Appendix 9) progressive disease, assessed by the investigator up to a maximum of 24 months from the date of first dose in Cycle 1, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides additional written informed consent prior to receiving additional study treatment. All other elements of the main consent, including description of reasonably foreseeable risks or discomforts or other alternative treatment options, will still apply.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the study and continue to receive monitoring according to Section 2. Radiographic assessment/scan(s) should continue in accordance with Section 2 and should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

For participants who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5-mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease.

It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and is therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.2 Post Study Treatment Study Follow-up

Poststudy 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 (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5.

Participants who discontinue study treatment may continue to be followed.

BMS may request that survival data be collected on all treated participants outside of the protocol-defined window (see Table 2-4). 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 3 documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before initiation of treatment. 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 laboratories until all study treatment-related toxicities resolve, return to baseline, or are deemed irreversible.

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

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 (Section 2).

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA20973M Imaging Manual provided by the central imaging vendor.

Screening and on-study images should be acquired as outlined in the Schedule of Activities (Section 2).

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

9.1.1.1 Methods of Measurement

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

If a participant has a contraindication for CT IV contrast, then 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.

If a participant has a contraindication for both MRI and CT IV contrasts, then 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.

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

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

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

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

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

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue, as described in Section 2, even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator using the RECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using the RECIST 1.1 criteria (see Appendix 9) for specifics on RECIST 1.1 criteria to be used in this study. Assessments of PR and CR must be confirmed by CT/MRI at least 4 weeks apart after initial documentation of response. A best overall response (BOR) of SD requires a minimum of 56 days on study from the date of first dose to the date of the first imaging assessment.

9.1.2 Patient-reported Outcomes

Not applicable.

9.2 Adverse Events

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

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Section 5.6 in the IB represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures for a minimum of 100 days after the last dose, except in cases where a study participant has started a new antineoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of first dose.

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

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

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

The method of evaluating and assessing the 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

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

All nonserious AEs and SAEs (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 after the last dose.

Every AE must be assessed by the investigator with regard to whether it is considered an IMAE. For events that are potentially immune mediated, additional information will be collected on the participant's CRF.

9.2.3 Follow-up of AEs and SAEs

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

All SAEs 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 toward 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.

The Sponsor or designee will report AEs 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 the BMS designee within 24 hours of awareness of the event and in accordance with the SAE reporting procedures described in Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS medical monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of the participant/Sponsor/IRB/EC, as applicable.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

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

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (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 DILI is defined as follows:

1) AT (ALT or AST) elevation > 3× ULN

AND

2) TBili > 2× 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 (ECG), x-ray filming, any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any accidental or intentional administration of any dose of a product that is considered both excessive and medically important will be considered an overdose. All occurrences of overdose must be reported as SAEs (see Section 9.2).

In the event of an overdose the investigator should:

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

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor, based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

Refer to the Schedule of Activities (Section 2).

9.4.2 Vital Signs

Refer to the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

Details regarding electrocardiograms are described in the Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Local laboratories will be used for the safety evaluations.
- A local laboratory will perform the analyses and will provide reference ranges for these tests. The clinical laboratory assessments are indicated in Table 9.4.4-1.
- Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- Results of all laboratory tests required by this protocol must be provided to BMS, recorded either on the laboratory pages of the CRF or by another mechanism, as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 9.2.6).

Table 9.4.4-1: Clinical Safety Laboratory Assessments

Hematology - Complete Blood Count	
• Hemoglobin	
• Hematocrit	
• Total leukocyte count, including differential	
• Platelet count	
Urinalysis (screening only)	
• Creatinine	
• Protein	
Chemistry	
• Aspartate aminotransferase (AST)	• Albumin (screening only)
• Alanine aminotransferase (ALT)	• Sodium
• Total bilirubin (TBili)	• Potassium
• Alkaline phosphatase (ALP)	• Chloride
• Lactate dehydrogenase (LDH)	• Calcium
• Creatinine	• Corrected calcium (screening only)
• Blood urea nitrogen (BUN) or serum urea	• Phosphorus
• Glucose	• Magnesium
Serology	
• Hepatitis B/C (screening only) (HBVsAg, HCV antibody or HCV RNA)	
• HIV, if mandated locally (see Appendix 8)	
Other Analyses	
• Thyroid stimulating hormone (TSH) with free thyroxine (fT3) and free triiodothyronine (fT4) (screening only)	
• TSH with reflexive fT3 and fT4	
• Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
• Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55	

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics

Not applicable.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the study is based on a Simon 2-stage design that will test whether retreatment with ipilimumab in combination with nivolumab in patients with mRCC progressing on maintenance nivolumab after first-line therapy with ipilimumab and nivolumab yields a DCR that is of clinical interest.

In this study, a DCR in excess of 20% will be considered of clinical interest. The Simon design will test the null hypothesis that the true DCR is less than or equal to 20% versus the alternative hypothesis that it exceeds 20%. The type I error rate will be 5% for a 1-sided test and the design will have 85% power to reject the null hypothesis when the true DCR is 35%.

The Simon design in this study requires 27 response-evaluable patients for the first stage. The patients included in the first stage analysis will be followed for at least 2 scans approximately 4 months after first dose. The enrollment will not be stopped during the first stage analysis so this relatively shorter follow-up period will be used in order to mitigate risk to patients being enrolled but not included in the first stage analysis. This analysis will quantify patients without progression. For example, confirmed responders, patients with unconfirmed response without progression, and patients with SD on consecutive scans would all qualify as having disease control. If there are exactly 27 patients in the first stage, then 7 or more of these patients, or at least 26%, will warrant proceeding to the second stage. Otherwise, enrollment will be stopped.

The enrollment will stop when either futility is declared at Stage 1 or once approximately 80 response-evaluable participants have been treated. Approximately 96 participants will be enrolled in order to obtain 80 response-evaluable patients, accounting for approximately 20% of

non-evaluable patients or withdrawal. The number of enrolled participants with SD ≥ 6 months will be capped at 50%.

The duration of the trial is expected to be approximately 24 months of treatment (Stage 1 + Stage 2) and 36 months of follow-up after the last participant first dosing. A futility analysis will be performed after Stage 1 and the primary analysis will be conducted upon completion of Stage 2.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and were registered into the IRT
Response Evaluable	All participants with baseline and at least 1 on-study tumor assessment who received at least 1 dose of study treatment. Analysis of demography, protocol deviations, baseline characteristics, and efficacy will be performed on this population.
Safety	All participants who take at least 1 dose of study treatment. This is the primary dataset for drug exposure and safety analysis.

Abbreviation: IRT = interactive response technology.

10.3 Statistical Analyses

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

A description of the participant population will be included in a statistical output report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	DCR is defined as the proportion of participants who achieve a confirmed best response of CR, PR, or SD for at least 6 months after first treatment dose using the RECIST 1.1. The number and percentage of participants in each category of BOR (CR, PR, SD, PD, or UTD) as per RECIST 1.1 criteria will be presented. An estimate of the response rate and an associated exact 2-sided 95% CI (Clopper and Pearson) will be presented.
Secondary	OS is defined as the time from first dose date to the date of death from any cause. For participants that are alive, their survival time will be censored at the date of last contact ("last known alive date"). OS will be censored for participants at the date of first dose if they were treated but had no follow-up. A similar analysis as in PFS will be conducted for OS.
	ORR is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST1.1 criteria.
	DOR is defined as the time between the date of first documented confirmed response (CR or PR) to the date of the first documented progression as per RECIST 1.1 or death due to any cause, whichever occurs first. For participants who neither progress nor die, the DOR will be

Endpoint	Statistical Analysis Methods
	censored at the same time they will be censored for the primary definition of PFS. DOR will be evaluated for responders (ie, participants with confirmed CR or PR) only.
	The primary definition of PFS is specified as the time between the date of first dose and the first date of documented progression as per RECIST 1.1 criteria or death due to any cause, whichever occurs first. Participants who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS. • Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. • Participants who did not have any on-study tumor assessments and did not die will be censored on their date of first dose. • Participants who receive subsequent systemic anticancer therapy prior to documented progression will be censored at the date of the last tumor assessment prior to the initiation of the new therapy. Median PFS will be estimated via the Kaplan-Meier product limit method. Two-sided 95% CI for the median PFS will be computed. Kaplan-Meier plots of PFS will be presented. The totality of PFS results will be presented in a single graphical display that includes the Kaplan-Meier curve and the median estimate and corresponding CIs. The secondary definition of PFS is defined as the time between the date of first dose and the first date of documented progression as per RECIST 1.1 criteria or death due to any cause, whichever occurs first. Participants who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the secondary definition of PFS. • Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. • Participants who did not have any on-study tumor assessments and did not die will be censored on their date of first dose. PFS based on investigator assessments will also be analyzed applying both the primary and the secondary definitions. More detail on PFS will be provided in a separate Statistical Analysis Plan.
	TTR is defined as the time from first dose date to the date of the first confirmed documented response (CR or PR) per RECIST 1.1 criteria. TTR will be evaluated for responders among the population of interest (ie, participants with a BOR of CR or PR).
[redacted]	

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; SD = stable disease; TTR = time to objective response; UTD = unable to determine

10.3.2 Safety Analyses

All safety analyses for nivolumab will be performed on the Safety Sample.

Endpoint	Statistical Analysis Methods
Secondary	The safety analysis will be performed in all treated participants. Descriptive statistics of safety will be presented using the NCI CTCAE version 5.0 by treatment arm. All AEs, drug-related AEs, SAEs, and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE version 5.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CCAE version 5.0 criteria. AE incident rate is defined as the proportion of participants with any grade AEs among treated participants. Events reported from the first dose and up to and including 100 days following the last dose of study treatment could be included in estimating this incidence rate.
[redacted]	

Abbreviations: AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event

10.3.3 Pharmacokinetic Analysis

Not applicable.

10.3.4 Other Analyses

10.3.4.1 Immunogenicity

Not applicable.

10.3.4.2 Outcomes Research Analyses

Not applicable.

10.3.5 Interim Analyses

A futility analysis will be performed after Stage 1 based on a Simon 2-stage design.

- In Stage 1, 27 response-evaluable patients will be enrolled and a futility analysis will be performed.
- In Stage 2 (if Stage 1 positive), 53 response-evaluable more patients will be enrolled.

If there are exactly 27 patients in the first stage, then 7 or more of these patients, or at least 26%, will warrant proceeding to the second stage. Otherwise, enrollment will be stopped.

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

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL	clearance
CLss	steady-state clearance
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTC	common terminology criteria
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CV%	% coefficient of variation
[redacted]	[redacted]
[redacted]	[redacted]
DILI	drug-induced liver injury
[redacted]	[redacted]
DOR	duration of response
DCR	disease control rate
ECG	electrocardiogram
eCRF	electronic case report form
eg	exempli gratia (for example)
eGRF	estimated glomerular filtration rate
[redacted]	[redacted]
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded

Term	Definition
fT3	free thyroxine
fT4	free triiodothyronine
GI	gastrointestinal
HBVsAg	hepatitis B virus antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible co-stimulator
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IMAE	immune-mediated adverse event
IMDC	International Metastatic RCC Database Consortium
IMP	investigational medicinal product
I-O	immuno-oncology
IP	investigational product
[redacted]	[redacted]
[redacted]	[redacted]
IRB	Institutional Review Board
IRRC	Independent Regulatory Review Commission
IRT	interactive response technology
ITSM	immunoreceptor tyrosine-based switch motif
I1	ipilimumab 1 mg/kg
I3	ipilimumab 3 mg/kg
IV	intravenous
IVRS	interactive voice response system
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
[redacted]	[redacted]
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
n	number of subjects or observations
N1	nivolumab 1 mg/kg
N3	nivolumab 3 mg/kg

Term	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OS	overall survival
ORR	objective response rate
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PPK	population pharmacokinetic
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
R&D	research and development
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TBili	total bilirubin
[redacted]	[redacted]
TSH	thyroid stimulating hormone
TTR	time to objective response
ULN	upper limit of normal
US	United States
UTD	unable to determine
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term "Participant" is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term "Subject" used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council f or Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

Subjects unable to give their written consent (eg, stroke or subjects 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 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 handwritten 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 nivolumab or ipilimumab (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 (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. 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.

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If...	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

The following minimal standards must be met:

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

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 AND PUBLICATIONS

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

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

- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

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

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 (eg, 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.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods)

- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

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

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 MANAGEMENT ALGORITHMS

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

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

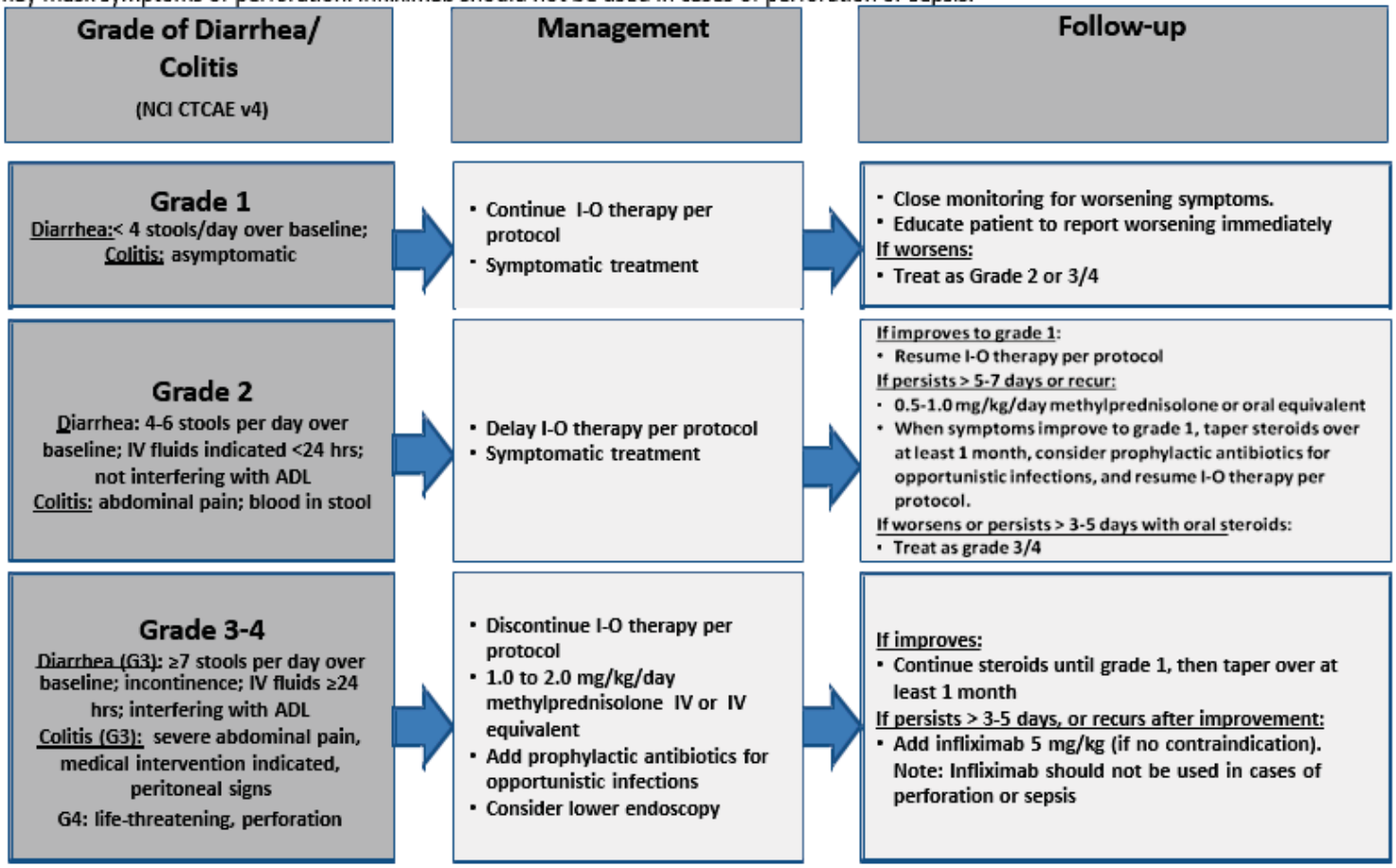
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

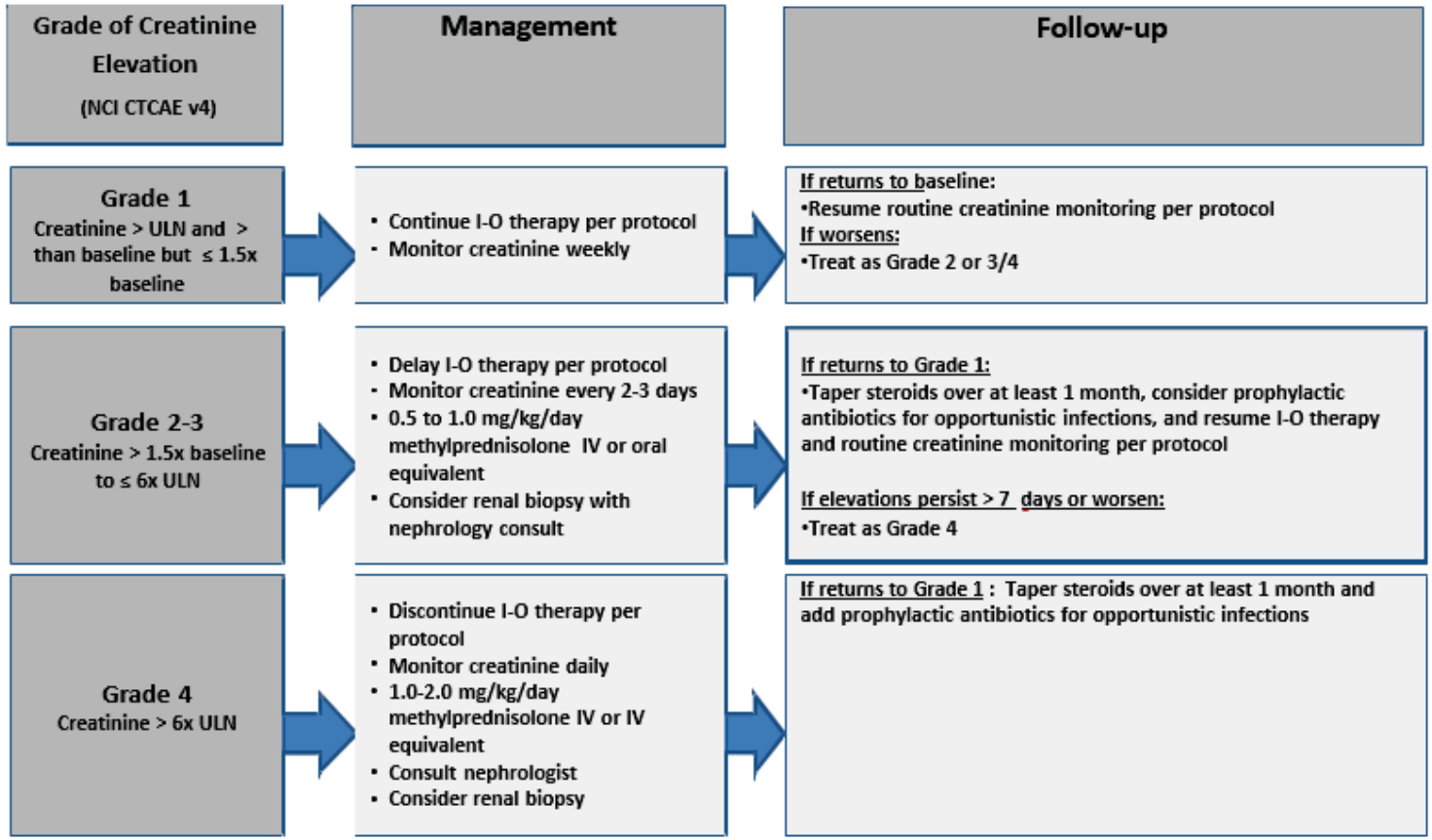


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Renal Adverse Event Management Algorithm

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

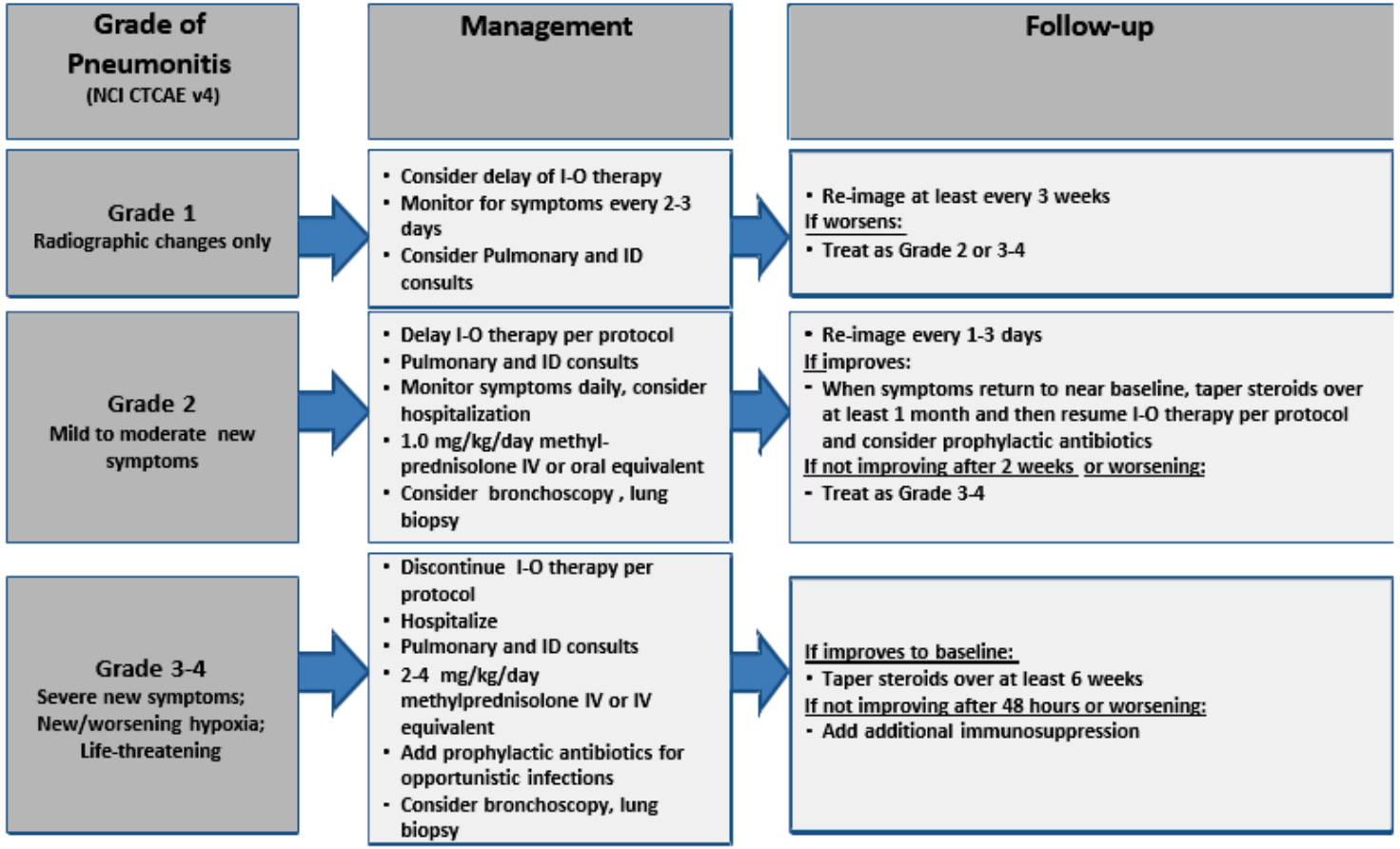


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

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



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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

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

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

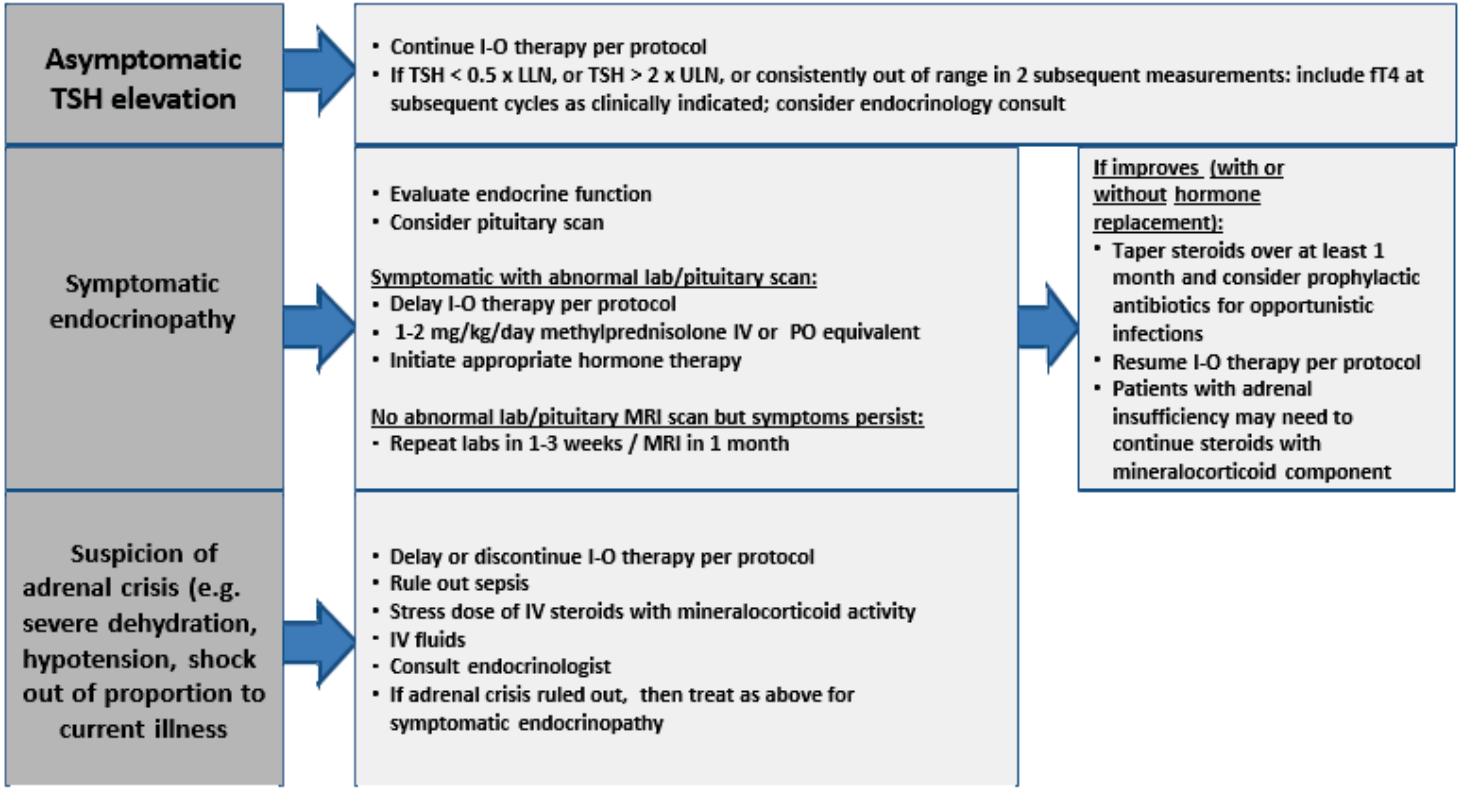
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

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

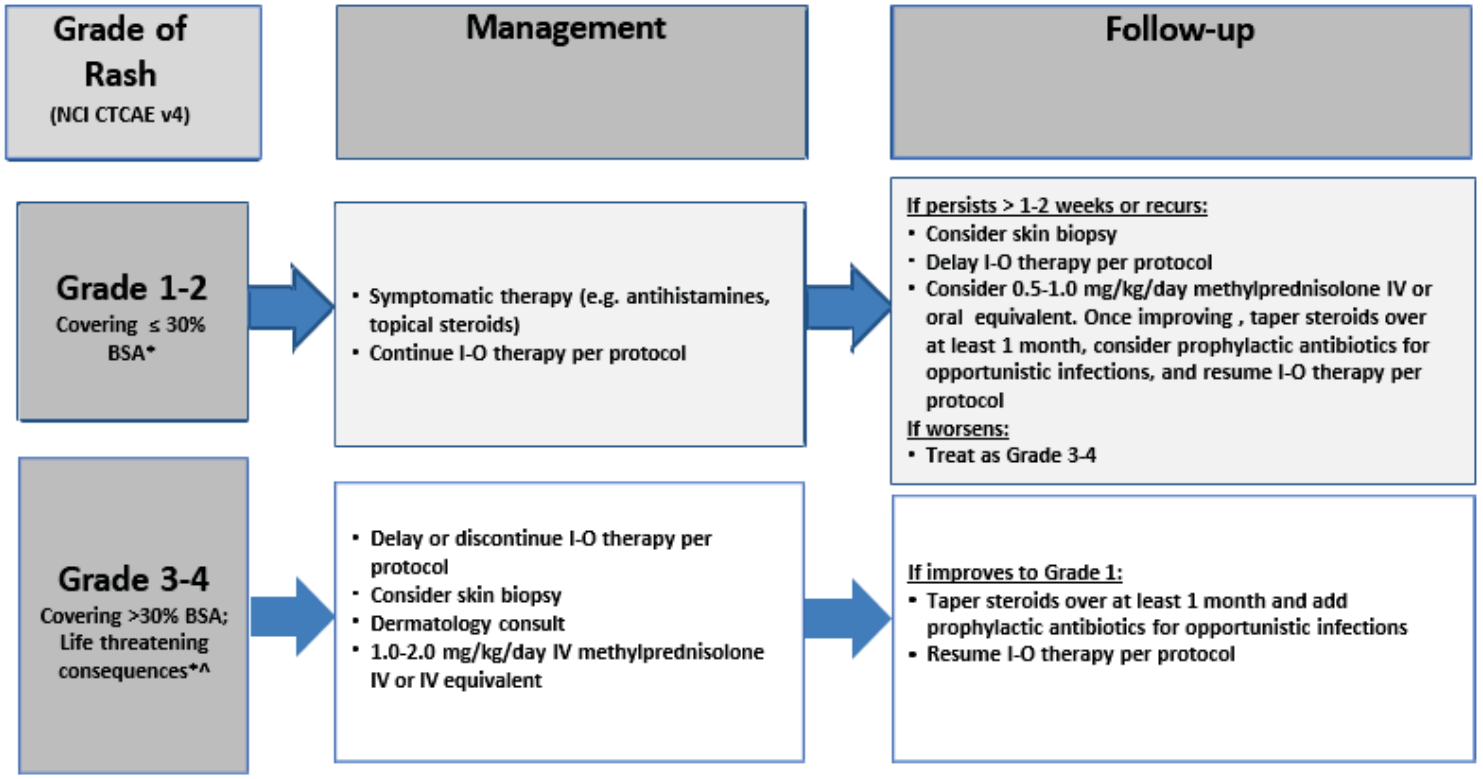


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

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



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

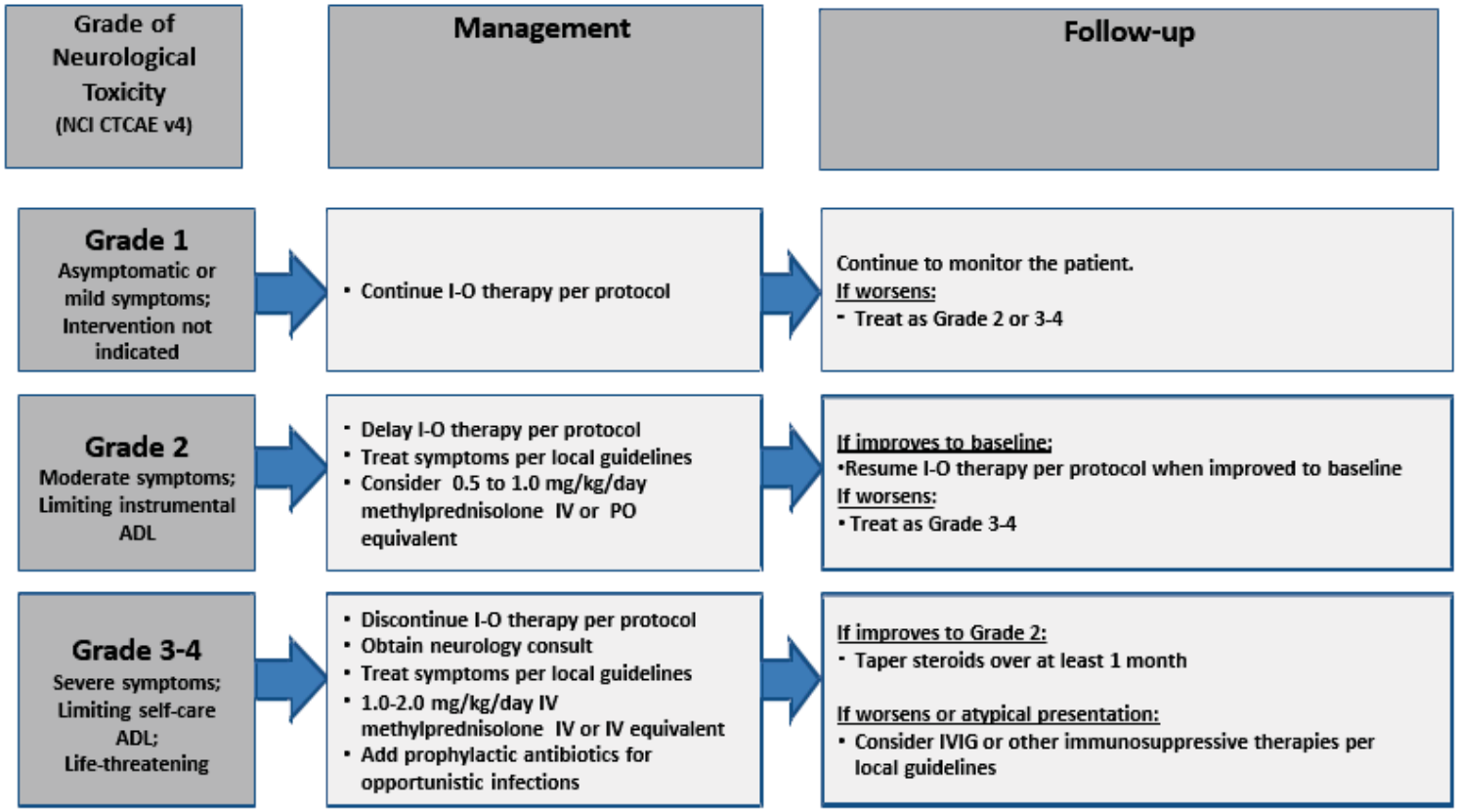
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2019

Neurological Adverse Event Management Algorithm

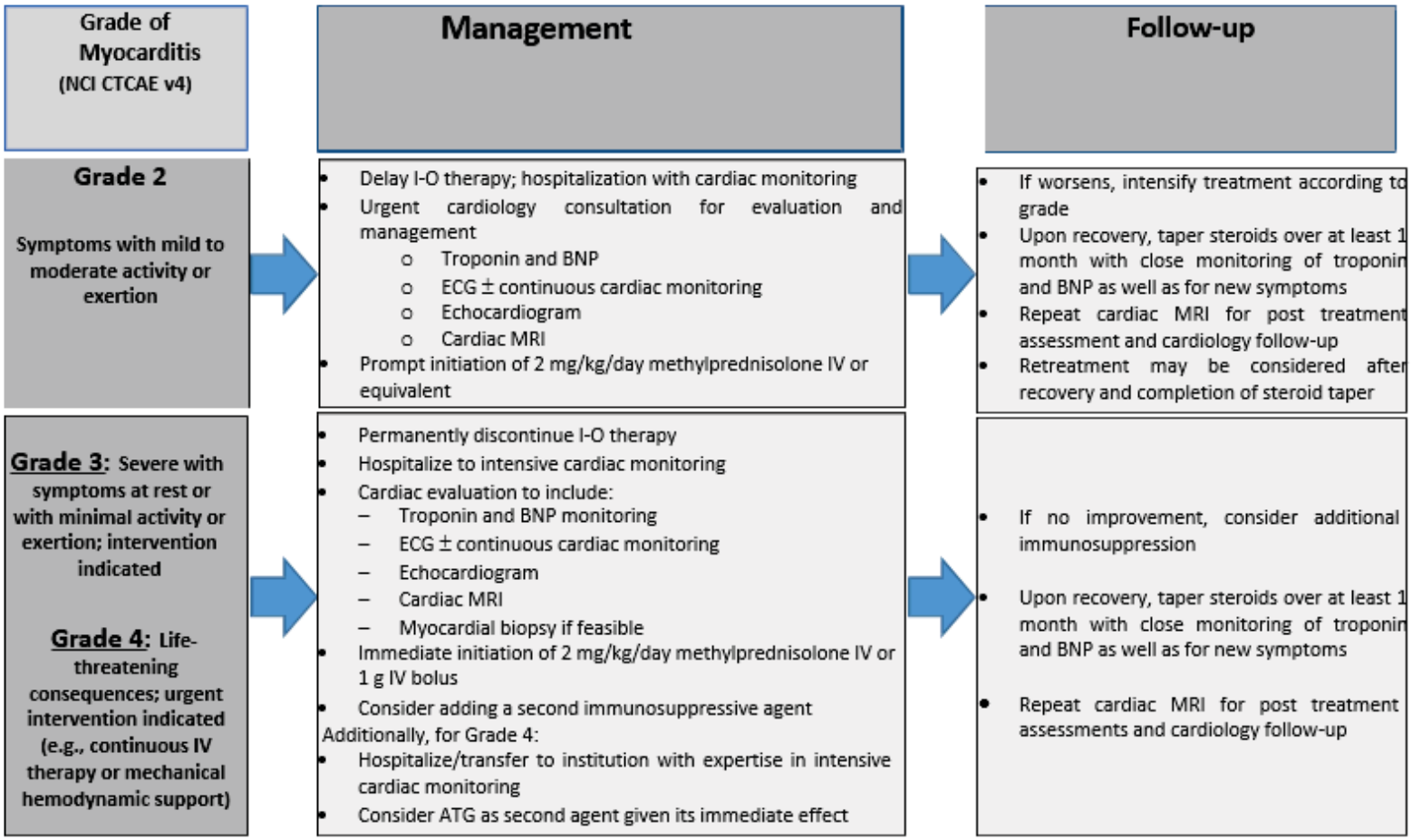
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

27-Jun-2019

Myocarditis Adverse Event Management Algorithm

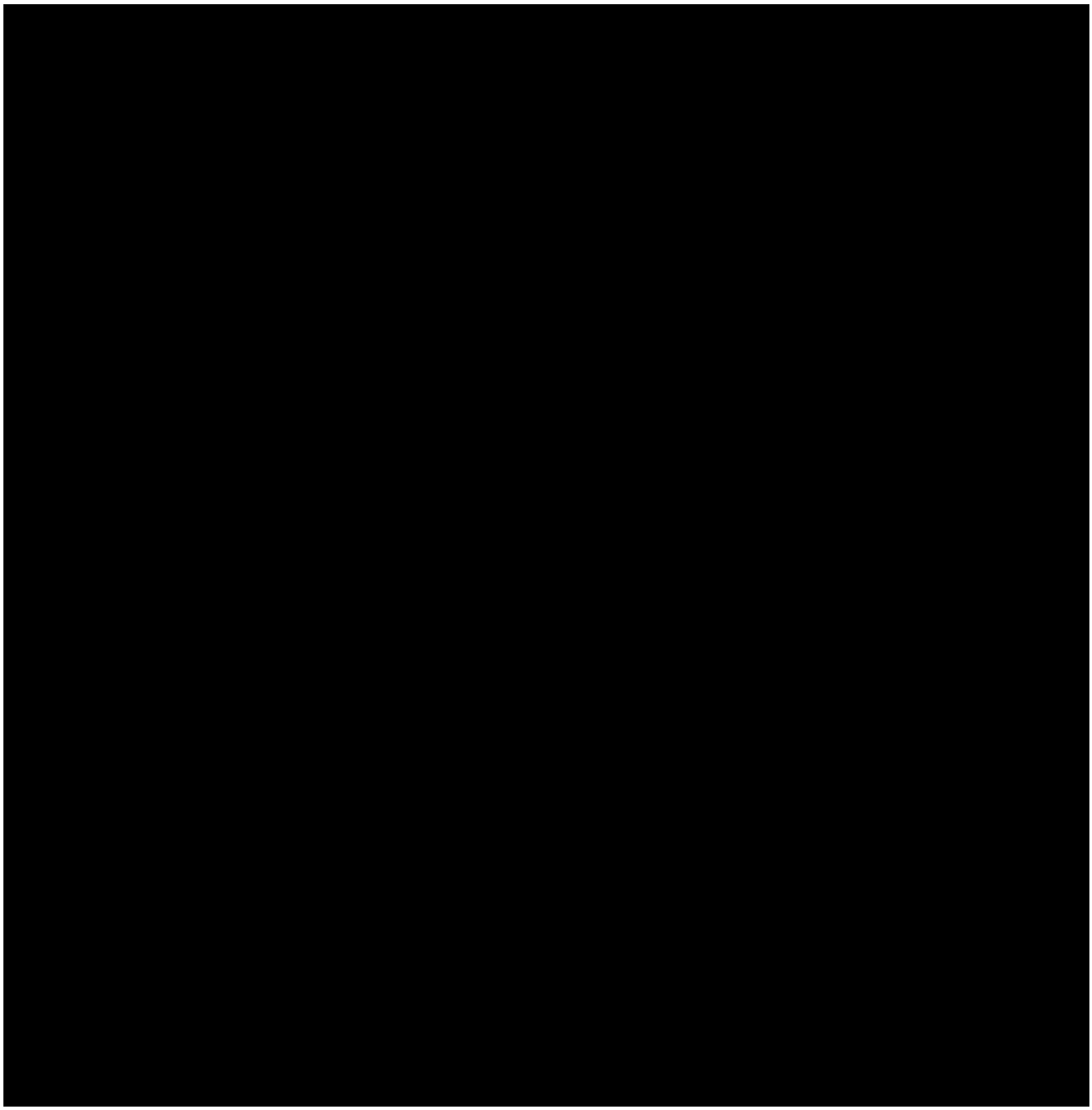


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019



APPENDIX 7 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

Any Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

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

APPENDIX 9 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [redacted].[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2× slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive

FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

1 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47