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Date 25-Oct-2016
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Clinical Protocol CA209800

Phase II, Randomized, Study of Multiple Administration Regimens for Nivolumab plus Ipilimumab in Subjects with Renal Cell Carcinoma

Revised Protocol Number: 02

Medical Monitor
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to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	02-Aug-2017	• Adding clarifications to the protocol • Correcting inconsistencies and text that was erroneously deleted in the Revised Protocol 01
Revised Protocol 01	18-Jan-2017	Incorporates Amendment 01
Amendment 01	18-Jan-2017	• Incorporate additional safety parameters and clarifications as per the FDA guidance following the submission of IND 132265 • Clarify inconsistencies in the original protocol as per the review of local Ethical Committees • Correct typo errors on the original protocol
Administrative Letter 01	16-Nov-2016	Delete one of the eligibility criteria in the protocol synopsis (and align it with the text in the eligibility criteria section of the protocol body) that was erroneously included in the original protocol
Original Protocol	25-Oct-2016	Not Applicable

[redacted]

Revised Protocol 02 will be applicable to all patients.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	• Exclusion Criteria 1 modified	Ensure consistency with protocol body language
Section 2: Schedule of Activities	• Timing for Vital Signs added; • Timing for MDSC highlighted; Duplicate Statements on Follow-Up Assessments deleted	There was an inconsistency across the Schedule of Activities with regards to the timing of those assessments.
Section 4 Objectives and Endpoints, Section 10.3.2, Safety Analyses	Timing of Primary Endpoint corrected to completion of Part 1.	Primary Endpoint Analysis adjusted as Primary Endpoint is related to safety of the combination dosing.
Section 7.4.3, Dose Discontinuation	Added Grade 3 “diarrhea, colitis, neurologic toxicity” as reasons for dose discontinuation	Text erroneously deleted from revised Protocol 01
Appendix 7, Performance Status Scales	Added comparative Table between ECOG and KPS	Change erroneously was not included in Revised Protocol 01
All	Minor clarifications, formatting and typographical corrections	Minor, therefore have not been summarized

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1 SYNOPSIS

Protocol Title: Phase II, Randomized, Study of Multiple Administration Regimens for Nivolumab plus Ipilimumab in Participants with Renal Cell Carcinoma

Study Phase: Phase II

[redacted]

Study Population:

The study population for this trial will include adult participants (≥ 18 years) with histological confirmation of RCC with a clear-cell component.

Key Inclusion Criteria:

- Histological confirmation of RCC with a clear-cell component
- Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC
- No prior systemic therapy for RCC with the following exception:
    - One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include a checkpoint inhibitor and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.
- Karnofsky Performance Status (KPS) of at least 70%
- Measurable disease as per RECIST 1.1 (investigator assessed)
- Tumor tissue (formalin-fixed paraffin-embedded (FFPE) archival or recent acquisition) must be received by the central vendor (block or unstained slides) in order to randomize a participant to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).
- Participants with favorable, intermediate and poor risk categories will be eligible for the study.
    - To be eligible for the Intermediate-Risk cohort one or two of the following prognostic factors as per International Metastatic RCC Database Consortium (IMDC) risk factors include:
        a) KPS equal to 70%
        b) Less than 1 year from diagnosis to randomization
        c) Hemoglobin less than the LLN
        d) Corrected calcium concentration greater than 10 mg/dL

e) Absolute neutrophil count greater than the ULN

f) Platelet count greater than the ULN

- If more than two factors are present they will be eligible for Poor-Risk cohort. If none of the above factors are present, participants are only eligible for the Favorable-Risk cohort.

Key Exclusion:

- Active brain metastases or leptomeningeal metastases. Baseline imaging of the brain is required within 28 days prior to randomization.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
- Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Participants with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.
- Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Uncontrolled adrenal insufficiency.
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
- Known medical 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 drug.
- Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.
- Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug.

- Any of the following laboratory test findings:
    a) WBC < 2,000/μL
    b) Neutrophils < 1,500/μL
    c) Platelets < 100,000/μL
    d) AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)
    e) Total Bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
    f) Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula).

Objectives and Endpoints:

Objective	Endpoint
Primary	
The primary objective is to evaluate the difference in safety between co-administered FRC nivolumab 3 mg/kg and ipilimumab 1 mg/kg relative to sequentially administered nivolumab 3 mg/kg and ipilimumab 1 mg/kg as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period.	The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as the number of participants who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated participants. The analysis of the primary endpoint will occur at the time of first (primary) analysis when all participants who are still on-treatment have had at least Part 1 period completed.
Secondary	
To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ	The first secondary endpoint is the incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination period (Part 1). This incidence rate will be defined similarly to the primary endpoint except that the event rate will be based on terms within the narrow scope SMQ rather than the broad scope.
To evaluate drug-related Grade 3 - 5 AE incidence rate defined using National Cancer Institute Common Terminology	The second secondary endpoint is the drug-related Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The drug-related Grade 3 - 5 AE rate is defined as number of participants who experienced at

Objective	Endpoint
Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria	least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants.
To evaluate all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria	The third secondary endpoint is the all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The all causality Grade 3 - 5 AE rate is defined as number of participants who experienced at least 1 AE of Grade 3 or higher with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants.
To determine PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab	The fourth secondary endpoint is PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab. PK will be measured using serum concentration-time data.
To evaluate the objective response rate (ORR), as determined by investigators	The fifth secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of participants with a BOR of CR or PR divided by the number of treated participants. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of first subsequent anti-cancer therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.
To evaluate progression free survival (PFS)	The sixth secondary endpoint is PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, 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.

Objective	Endpoint
	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 randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anti-cancer therapy.

Overall Design:

Study Design and Duration:
This is a Phase 2, open-label, randomized 2-arm study of the fixed ratio combination (BMS-986237) of nivolumab and ipilimumab in a 3:1 ratio (nivolumab 3 mg/kg and ipilimumab 1 mg/kg). The study is divided into two parts.

In Part 1, Arm A, BMS-986237 will be administered as one 60-minute infusion, every 3 weeks for up to 4 doses.

In Part 1, Arm B, nivolumab and ipilimumab will be administered sequentially within the same day, as two separate infusions, one 60-minute nivolumab infusion and one 30-minute ipilimumab infusion with a 30-minute break between each infusion, every 3 weeks for up to 4 doses.

Six weeks after the last dose in Part 1, participants will then receive nivolumab 480 mg flat dose infused over 30 minutes every four weeks in Part 2 until progression or unacceptable toxicity.

Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity whichever comes first.

Safety of subjects will be monitored on an ongoing basis by the study team. The BMS medical monitor is a physician who is responsible for reviewing the safety of patients in this study in a systematic and continuous manner. This includes a review of serious and non-serious adverse events including all hematological and non-hematological events.

In addition, study safety is evaluated on an ongoing basis by representatives of BMS Global Pharmacovigilance and the BMS medical safety team (MST), who operate independently from the clinical team and monitor safety across all nivolumab protocols, identify potential safety signals, notify appropriate stakeholders of relevant findings, and implement risk management plans.

Number of Participants:

Enrolled: Approximately 129 participants

Randomized: 102 *(to yield 100 treated, assuming 1.5% attrition)*

Screen Failure Rate: It is expected that approximately 129 participants will need to be enrolled in order to randomize 102, assuming a screen failure rate of 21%.

This number of treated participants was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the two treatment arms. Fifty treated participants per arm will allow estimation of the rate difference within 95% confidence limits of ± 20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk. The 20% limit represents what is considered to be a clinically meaningful difference in the rates of infusion-related reactions.

Treatment Arms and Duration:

Study treatment: This trial is a two-arm, open-label, randomized study:

Part 1:

- **Treatment Arm A:** FRC single infusion (mix of nivolumab and ipilimumab in 3:1 ratio in that order) administered intravenously over 60 minutes
- **Treatment Arm B:** nivolumab (3 mg/kg infused over 60 minutes) followed by ipilimumab (1 mg/kg infused over 30 minutes) administered intravenously with a 30-minute interval waiting period between the two separate infusions
- Note: Cycles will be defined as three weeks in the combination period, Part 1

Part 2:

- Following four doses of the combination participants will switch to nivolumab 480 mg flat dose infused over 30 minutes q 4 weeks. There will be a 6-week interval wait time after the completion of the 4 combination doses prior to beginning the nivolumab monotherapy.
- Note: Cycles will be defined as four weeks in the flat dosing period, Part 2

Discontinuation of Participants from Treatment:

Participants who advance to Part 2 will be treated for up to disease progression or unacceptable toxicity, whichever comes first. Once a patient has discontinued from treatment, he or she will continue to be followed for overall survival (OS) for approximately 5 years. All reasonable effort will be made to maintain contact with participants during this follow-up period via phone calls, faxes, or emails.

If investigator's use of a third-party representative to assist in locating participants that have been lost to follow up 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.

Post Study Drug Access to Therapy:

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by a responsible health authority; b) the study is terminated due to safety concerns; c) the participant can obtain medication from a government sponsored or private health program; or therapeutic alternatives become available in the local market.

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

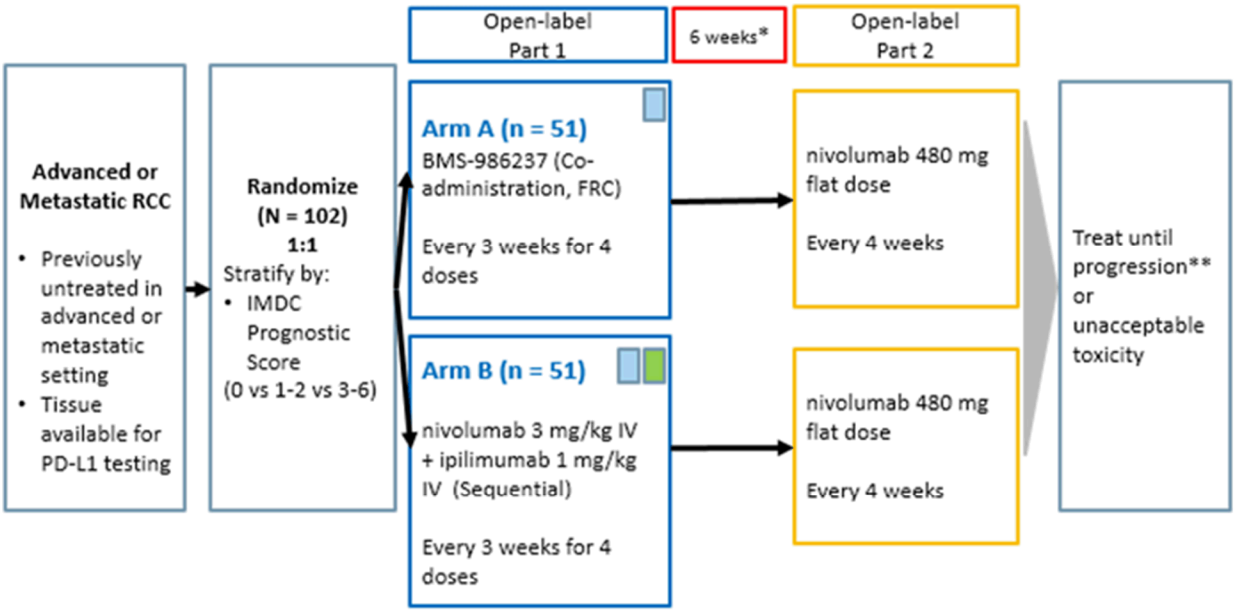
The fixed ratio combination drug product is formulated by combining the nivolumab drug substance and ipilimumab drug substance at a nivolumab/ipilimumab protein-mass ratio of 3 to 1. The composition and manufacturing process of these 2 drug substances are the same as those used for the nivolumab and ipilimumab commercial drug products.

The Sponsor has conducted quality testing to demonstrate that no interaction occurs between the two antibodies. The table below provides the composition of the three products.

Nivolumab/Ipilimumab 3:1 for Renal Cell Carcinoma

Component	Nivolumab	Ipilimumab	Fixed Combination
Nivolumab	10 mg/mL		8.57 mg/mL
Ipilimumab		5 mg/mL	2.85 mg/mL
Sodium Citrate	20 mM		8.57 mM
Tris Hydrochloride		20 mM	11.43 mM
Sodium Chloride	50 mM	100 mM	78.57 mM
Mannitol	3% w/v	1% w/v	1.86% w/v
Pentetic Acid	20 μM	100 μM	65.7 μM
Polysorbate 80	0.02% w/v	0.01% w/v	0.023% w/v

The study design schematic is presented in the figure below. The duration of the trial is expected to be 6 months of accrual and approximately 60 months of follow-up after the last participant has received the first study drug dose. The primary analysis is only for safety related endpoint and will be conducted when all participants who remain on-treatment have completed Part 1. The final analysis will be for efficacy related endpoints and be conducted after all participants have at least 9 months of follow-up.



*6 weeks from last combination dose in Part 1 to first nivolumab monotherapy dose in Part 2
**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA209800)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures register in IRT to obtain participant number
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Medical History	X	Including concomitant medications and prior medications for collection of prior cancer therapy
Tumor Tissue Samples	X	Sufficient tumor tissue, archival or recent acquisition, (block or a minimum of 20 slides is requested with a minimum of 10 slides required; obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) confirmed to be available at Central Laboratory.
Safety Assessments		
Physical Examination	X	
Vital Signs	X	BP, HR, temperature, within 14 days prior to randomization
Physical Measurements (including performance status)	X	Height, weight, IMDC score, BSA and Karnofsky Performance Status.
Assessment of Signs and Symptoms	X	For screening, within 14 days prior to 1st dose
Serious Adverse Events Assessment	Continuously	Serious Adverse Events from time of consent
Review of Concomitant Medications	X	Within 14 days prior to randomization

Table 2-1: Screening Procedural Outline (CA209800)

Procedure	Screening Visit	Notes
Laboratory Tests	X	CBC with differential, Chemistry panel including: LDH, AST, ALT, ALP, ALB, T.Bili, BUN or serum urea level, creatinine, corrected Ca, Na, K, Cl, Glucose, amylase, lipase, phosphate, TSH, Free T4, Free T3, within 14 days of randomization; hepatitis B surface antigen (HBVsAg), and hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), within 28 days of randomization
Pregnancy Test (WOCBP only)	X	Serum or urine (minimum sensitivity equivalent units 25IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment.
Screening/Baseline Tumor Assessment	X	Chest, Abdomen, Pelvis, and Brain within 28 days prior to first dose. Head MRI is required in participants with known history of brain metastases; participants without known history of brain metastases may have head CT or MRI Contrast enhanced CT scan of the chest, abdomen and pelvis and all other known/suspected sites of disease. Should a participant have contraindication for CT intravenous contrast, a non-contrast CT scan of the chest and a contrast enhanced MRI of the abdomen and pelvis and all other known/suspected sites of disease. For participants with known brain metastasis, an MRI brain without and with gadolinium is required at Screening. A brain CT is not allowed for participants with a history or evidence of known brain metastasis at Screening.
Clinical Drug Supplies		
Randomize	X	First dose to be administered within 72 hours following randomization.

Table 2-2: On-Study Assessments Part 1 (CA209800)

Procedure	For Part 1, Study treatment Every 3 Weeks for 4 Doses (Both Arm A and Arm B)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and temperature within 72 hours prior to dosing
Physical Measurements (including performance status)	X	Weight and KPS within 72 hours prior to dosing
Adverse Events Assessment	Continuously	For 48 hours, pay close attention to any hypersensitivity, anaphylaxis or any infusion related reactions.
Review of Concomitant Medications	X	
Laboratory Tests	X	Within 72 hrs prior to dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, corrected Ca, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate, TSH (+ reflex Free T4 and Free T3)
Pregnancy Test (WOCBP only)	X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose and every 3 weeks thereafter in Part 1 of the study. A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	X	Refer to Table 9.5-1

Table 2-2: On-Study Assessments Part 1 (CA209800)

Procedure	For Part 1, Study treatment Every 3 Weeks for 4 Doses (Both Arm A and Arm B) Cycle 1, 2, 3, 4 (Day 1)	Notes
PK Samples	X	Refer to Table 9.5-1
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Efficacy Assessment		
Tumor Assessment	See Notes	FIRST tumor assessment should be performed at 12 weeks (± 1 week) following randomization (until disease progression or treatment discontinuation, whichever occurs later). Contrast enhanced CT Chest, CT (or MRI with and without contrast) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI (with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated (until disease progression or treatment discontinuation, whichever occurs later)

Table 2-2: On-Study Assessments Part 1 (CA209800)

Procedure	For Part 1, Study treatment Every 3 Weeks for 4 Doses (Both Arm A and Arm B)	Notes
	Cycle 1, 2, 3, 4 (Day 1)	
Outcomes Research Assessments		
FACT-G, EQ-5D-3L, and FKSI-19	X	To be completed at the start of the clinic visit every 6 weeks. First questionnaire should be completed after randomization but before dosing. (Cycle 1, 3)
Health Care Utilization	X	Health Care Utilization will be collected at each visit
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	Within 24 hours prior to dosing
Administer Study Treatment	X	First dose to be administered within 72 hours following randomization.

Table 2-3: On-Study Assessments - Part 2 (CA209800)

Procedure	For Part 2, Study treatment is Administered Every 4 Weeks (Both Arm A and Arm B) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4
Safety Assessments		
Targeted Physical Examination	X	To be performed only if clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, and temperature within 72 hours prior to dosing
Physical Measurements (including performance status)	X	Weight and KPS within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Beginning at Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc.), on-study local laboratory assessments should be done within 72 hours prior to dosing and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, corrected Ca, Na, K, Cl, LDH, glucose, amylase, lipase, phosphate, TSH with reflexive Free T4, Free T3. Beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc.), on-study local laboratory assessment should be done within 72 hours prior to dosing and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Pregnancy Test (WOCBP only)	X	Serum or urine (minimum sensitivity equivalent units 25IU/L or equivalent units of HCG) every 4 weeks. A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
Outcomes Research Assessments		
FACT-G, EQ-5D-3L, and FKSI-19	X	To be completed at the start of the clinic visit every 4 weeks from Cycle 5 onwards
Health Care Utilization	X	Health Care Utilization will be collected at each visit from Cycle 5 onwards

Table 2-3: On-Study Assessments - Part 2 (CA209800)

Procedure	For Part 2, Study treatment is Administered Every 4 Weeks (Both Arm A and Arm B) Cycle 5 and beyond (Day 1)	Notes Cycle 5 will begin 6 weeks after Cycle 4
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	X	Refer to Table 9.5-1
PK Samples	X	Refer to Table 9.5-1
Efficacy Assessment		
Tumor Assessment	See Notes	First tumor assessment during Part 2 should occur after 8 weeks (± 1 week) relative to previous tumor assessment performed at Week 12. Subsequent tumor assessments should occur every 8 weeks (± 1 week) for the first 12 months from randomization. From the second year from randomization, tumor assessments should occur every 12 weeks (± 2 weeks) until disease progression or treatment discontinuation, whichever occurs later. Contrast enhanced CT Chest, CT (or MRI with and without contrast)) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI brain with and without gadolinium approximately every 12 weeks, or sooner if clinically indicated (until disease progression or treatment discontinuation, whichever occurs later).
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Administer Study Treatment	X	Note: Within 72 hours from vial assignment, the participant must receive the dose of study medication.

Table 2-4: Follow-up Assessments (CA209800)

Procedure	Follow Up,[a] Visits X1 and X2	Survival,[b] Follow-up Y Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study treatment related issues
Adverse Event Assessments	X	X	
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN, creatinine, amylase, lipase and TSH (+ reflex Free T4 and Free T3) for X1, repeat at X2 if study treatment related toxicity persists.
Pregnancy Test (WOCBP Only)	X		Serum or urine
Review of Concomitant Medications	X		
Pharmacokinetic Samples and Immunogenicity Assessments			
PK Samples	X		Refer to Table 9.5-1
Immunogenicity blood sample	X		Refer to Table 9.5-1
Survival Status			
Participant Status	X	X	Every 3 months, Survival Follow up Visits may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy
Efficacy Assessments			
Tumor Assessments	See Notes		Only for participants without progression on study therapy. SUBSEQUENT tumor assessments should continue to occur every 8 weeks (± 1 week) thereafter for the first 12 months, then every 12 weeks (± 2 weeks) until disease progression or treatment discontinuation, whichever occurs later. Contrast enhanced CT Chest, CT (or MRI with and without contrast) abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Participants with a history of brain metastasis should have surveillance MRI

Table 2-4: Follow-up Assessments (CA209800)

Procedure	Follow Up,[a] Visits X1 and X2	Survival,[b] Follow-up Y Visits	Notes
			Brain without and with gadolinium approximately every 12 weeks, or sooner if clinically indicated (until disease progression or treatment discontinuation, whichever occurs later).
Outcomes Research Assessments			
FACT-G and FKSI-19	X		Collection done at X1 and X2 only
EQ-5D-3L	X	X	Collection done during X1 and X2. Survival follow-up every 3 months for the first year and 6 months thereafter
Health Care Utilization	X		Collection done at X1 and X2 only
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

[a] X visits occur as follows - X1 = 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose, X2 = 84 days (± 7 days) from follow-up visit 1. Follow up visits X1 and X2 will occur only after participant completes all study treatment. Participants must be followed for at least 100 days after last dose of study treatment.

[b] Y Survival visits = every 3 months from X2 (± 7 days). Survival Follow-up visits to occur every 3 months from Follow-up Visit 2. 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 contacts.

For responders (CR, PR or SD) on study beyond 2 years an extension of the frequency of scans from every 12 weeks to every 24 weeks until disease progression or treatment discontinuation, whichever occurs later, is permitted. Participants who discontinue study therapy for reasons other than progression should continue to be scanned until disease progression is documented.

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

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate the difference in safety between co-administered FRC nivolumab 3 mg/kg and ipilimumab 1 mg/kg relative to sequentially administered nivolumab 3 mg/kg and ipilimumab 1 mg/kg as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period.	The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as the number of participants who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated participants. The analysis of the primary endpoint will occur at the time of first (primary) analysis when all participants who are still on-treatment have had at least Part 1 period completed.
Secondary	
To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ	The first secondary endpoint is the incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination period (Part 1). This incidence rate will be defined similarly to the primary endpoint except that the event rate will be based on terms within the narrow scope SMQ rather than the broad scope.
To evaluate drug-related Grade 3 - 5 AE incidence rate defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria	The second secondary endpoint is the drug-related Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The drug-related Grade 3 - 5 AE rate is defined as number of participants who experienced at least 1 AE of Grade 3 or higher, judged to be related to study treatment by the investigator, with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants.
To evaluate all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria	The third secondary endpoint is the all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The all causality Grade 3 - 5 AE rate is defined as number of participants who experienced at least 1 AE of Grade 3 or higher with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
To determine PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab.	The fourth secondary endpoint is PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab. PK will be measured using serum concentration-time data.
To evaluate the objective response rate (ORR), as determined by investigators	The fifth secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of participants with a BOR of CR or PR divided by the number of treated participants. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of first subsequent anti-cancer therapy including radiotherapy, tumor-directed surgery, or systemic anticancer therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.
To evaluate progression free survival (PFS)	The sixth secondary endpoint is PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, 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. 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 randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anti-cancer therapy including radiotherapy, tumor directed surgery, or systemic anticancer therapy.
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5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2, open-label, randomized 2-arm study of the fixed ratio combination (BMS-986237) of nivolumab and ipilimumab in a 3:1 ratio (nivolumab 3 mg/kg and ipilimumab 1 mg/kg) in participants with previously untreated advanced or metastatic RCC.

Participants meeting all eligibility criteria will be randomized 1:1 ratio and stratified by IMDC prognostic score (0 vs 1-2 vs 3-6) to Arm A (BMS-986237) or Arm B (nivolumab and ipilimumab administered sequentially).

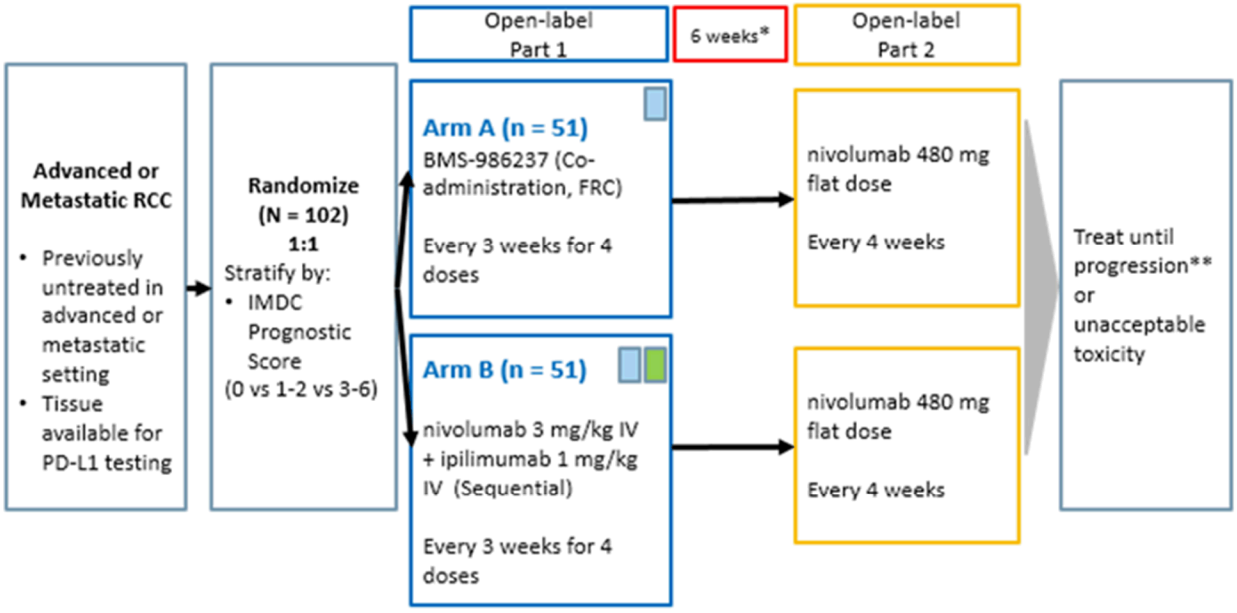
In Part 1, Arm A, BMS-986237 will be administered as one 60-minute infusion, every 3 weeks for up to 4 doses.

In Part 1, Arm B, nivolumab and ipilimumab will be administered sequentially within the same day, as 2 separate infusions, one 60-minute nivolumab infusion and one 30-minute ipilimumab infusion with a 30 minute break between each infusion, every 3 weeks for up to 4 doses.

Six weeks after the last dose in Part 1, participants will then receive nivolumab 480 mg flat dose infused over 30 minutes every four weeks in Part 2 until progression or unacceptable toxicity. Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity, whichever comes first.

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

Figure 5.1-1: Study Design Schematic



*6 weeks from last combination dose in Part 1 to first nivolumab monotherapy dose in Part 2
**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

Physical examinations, vital sign measurements and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

It is expected that approximately 129 participants will need to be enrolled in order to randomize 102, assuming a screen failure rate of 21%.

This number of 100 treated participants was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA

Anaphylactic Reaction SMQ between the two treatment arms. Fifty treated participants per arm will allow estimation of the rate difference within 95% confidence limits of ± 20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk. The 20% limit represents what is considered to be a clinically meaningful difference in the rates of infusion-related reactions.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. The end of the trial is defined as the last scheduled procedure shown in the time and events schedule for the last participant who has received combination treatment. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

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

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6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests including the completion of quality of life questionnaires and other requirements of the study

2) Type of Participant and Target Disease Characteristics

a) Histological confirmation of RCC with a clear-cell component

b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC

c) No prior systemic therapy for RCC with the following exception:

   i. One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include a checkpoint inhibitor and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

d) Karnofsky Performance Status (KPS) of at least 70%

e) Measurable disease as per RECIST 1.1

f) Tumor tissue (formalin-fixed paraffin-embedded (FFPE) archival or recent acquisition) must be received by the central vendor (block or unstained slides) in order to randomize a participant to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).

   i. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses

g) Participants with favorable, intermediate and poor risk categories will be eligible for the study.

   i. To be eligible for the Intermediate-Risk cohort one or two of the following prognostic factors as per International Metastatic RCC Database Consortium (IMDC) risk factors include:

      i. KPS equal to 70%

      ii. Less than 1 year from initial diagnosis to randomization

      iii. Hemoglobin less than the LLN

      iv. Corrected calcium concentration greater than 10 mg/dL

      v. Absolute neutrophil count greater than the ULN

      vi. Platelet count greater than the ULN

   ii. If more than two factors are present they will be eligible for Poor-Risk cohort. If none of the above factors are present, participants are only eligible for the Favorable-Risk cohort.

3) Age and Reproductive Status

a) Males and Females, ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment. Women must not be breastfeeding

c) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. WOCBP should therefore use an adequate method

to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo approximately five half lives) after the last dose of investigational drug (combination or monotherapy).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 90 days plus the time required for the investigational drug to undergo approximately five half-lives. Men who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug (combination or monotherapy). In addition, male participants must be willing to refrain from sperm donation during this time.

e) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in 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. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4 which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI - except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration.

b) Ocular melanoma

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

d) 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

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

f) Known medical 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 treatment administration or interfere with the interpretation of safety results.

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

h) Anti-cancer therapy less than 28 days prior to the first dose of study treatment or palliative, focal radiation therapy less than 14 days prior to the first dose of study treatment.

i) Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study treatment.

2) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

b) Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Participants with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.

c) Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study treatment. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

d) Uncontrolled adrenal insufficiency.

3) Physical and Laboratory Test Findings

a) Any of the following laboratory test findings:

i. WBC < 2000/μL
ii. Neutrophils < 1500/μL
iii. Platelets < $100*10^3$/μL
iv. Hemoglobin < 9.0 g/dL
v. Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)
vi. AST/ALT: > 3.0 x ULN
vii. Total bilirubin > 1.5 x ULN (participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)
viii. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study treatment components

5) Other Exclusion Criteria

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

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

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

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

Laboratory parameters and/or assessments that are included in 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 both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP).

In this protocol, investigational products are:

- Nivolumab
- Ipilimumab

- Nivolumab/Ipilimumab Fixed Ration Combination (FRC).

The fixed ratio combination drug product is formulated by combining the nivolumab drug substance and ipilimumab drug substance at a nivolumab/ipilimumab protein-mass ratio of 3 to 1.

The Sponsor has conducted quality testing to demonstrate that no interaction occurs between the two antibodies. The table below provides the composition of the three products.

Table 7-1: Nivolumab/Ipilimumab 3:1 for Renal Cell Carcinoma

Component	Nivolumab	Ipilimumab	Fixed Combination
Nivolumab	10 mg/mL		8.57 mg/mL
Ipilimumab		5 mg/mL	2.85 mg/mL
Sodium Citrate	20 mM		8.57 mM
Tris Hydrochloride		20 mM	11.43 mM
Sodium Chloride	50 mM	100 mM	78.57 mM
Mannitol	3% w/v	1% w/v	1.86% w/v
Pentetic Acid	20 μM	100 μM	65.7 μM
Polysorbate 80	0.02% w/v	0.01% w/v	0.023% w/v

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Table 7-2: Study treatments for CA209800					
Product Description / Class and Dosage Form	**Potency**	**Primary Packaging (Volume)/Label Type**	**Secondary Packaging (Qty)/Label Type**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab Solution for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	10 mL per vial Or 4 mL vial/Open label	5 or 10 vials per carton/ Open-label Or 240 mg kits (2 - 100 mg vials & 1 - 40 mg vial)	Clear to opalescent colorless to pale yellow liquid. May contain particles	2°C to 8°C. Protect from light and freezing
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2°C to 8°C. Protect from light and freezing
BMS-986237 Solution for Injection (Nivolumab/Ipilimumab FRC)	240 mg Nivolumab/ 80 mg Ipilimumab	28 mL per vial/Open-label **(vial with booklet label - first page in ORANGE)**	6 vials per carton/Open-label	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present	2°C to 8°C. Protect from light and freezing

7.1 Treatments Administered

7.1.1 Part 1 Study Treatment Administration

In Part 1 of the study there will be two treatment arms:

Arm A BMS-986237 (nivolumab 3 mg/kg/ipilimumab 1 mg/kg as a single infusion) will be administered as one 60-minute infusion on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Arm B nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 30-minute ipilimumab infusion with a 30-minute break between each infusion. Nivolumab is to be administered first. Participants should receive nivolumab at a dose of 3 mg/kg as a 60-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

The second infusion will always be ipilimumab, and the time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Participants should receive ipilimumab at a dose of 1 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate 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.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the next infusion.

Both agents given as single agents are uncommonly associated with infusion reactions, incidence less than 1% for ipilimumab (Yervoy® FDA Label) and for nivolumab 3% (Opdivo® FDA Label). In the CA209069 study, hypersensitivity/infusion reactions were listed as 3.2% for the combination and 2.2% for ipilimumab. No Grade 3 or Grade 4 hypersensitivity/infusion reactions were observed in either the combination or single agent ipilimumab treatment groups.[28]

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

The **pharmacy manual** includes detailed instructions for study medication preparation.

During Part 1, participants may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

In extenuating circumstances in which the participant cannot make the dosing schedule within the 3-day window, BMS Medical Monitor should be contacted.

Detailed instructions for dilution and infusion of study treatment injection are provided in the pharmacy binder, pharmacy reference sheet and current investigator brochures. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 Part 2 Study Treatment Administration

Starting 6 weeks after the last co-administered dose in Part 1, participants will be administered a flat dose 480 mg nivolumab 30-minute infusion every 4 weeks (Q4W) until unacceptable toxicity or disease progression is reached, whichever comes first.

Participants may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Every effort should be made to adhere to protocol treatment schedule of administration of nivolumab every 4 weeks in the maintenance phase. In extenuating circumstances in which the participant cannot make the dosing schedule within the 3-day window, BMS Medical Monitor should be contacted.

Note: Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity, whichever comes first.

For details on prepared drug storage, preparation, and administration, please refer to the nivolumab, ipilimumab and BMS-986237 IBs and/or pharmacy reference sheets. The selection and timing of dose for each participant is as follows:

7.1.3 Selection and Timing of Dose

Table 7.1.3-1: Selection and Timing of Dose Part 1 (Arm A) (Administered as one 60-minute infusion, every 3 weeks for up to 4 doses).

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986237	4 mg/kg	Every 3 Weeks (4 total doses)	IV

Table 7.1.3-2: Selection and Timing of Dose Part 1 (Arm B) - (Administered sequentially within the same day, as two separate infusions, one 60-minute nivolumab infusion and one 30-minute ipilimumab infusion with a 30 minute break between each infusion, every 3 weeks for up to 4 doses)

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
nivolumab	3 mg/kg	Every 3 Weeks (4 total doses)	IV
ipilimumab	1 mg/kg	Every 3 Weeks (4 total doses)	IV

Table 7.1.3-3: Selection and Timing of Dose Part 2 (All Participants) - (Administered as infusion over 30 minutes every four weeks in Part 2 until progression or unacceptable toxicity)

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
nivolumab	480 mg	Every 4 weeks	IV

When nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush 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, filters changed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

There will be no dose escalations or reductions of study treatment allowed. 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 study treatment administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.5.

Doses of nivolumab, ipilimumab, and BMS-986237 may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab injection is to be administered as a ~ 60-minute IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the

protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection are provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

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

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

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

BMS-986237 injection is to be administered as an IV infusion through a 0.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Prior to infusion, the BMS-986237 injection is diluted with 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) to required concentrations.

BMS-986237 is available as a solution at a concentration of 11.4 mg/mL. The volume for calculated weight based dose (refer to pharmacy reference sheets) is to be added to 40 mL of 0.9% Sodium Chloride (normal saline) USP prior to being administered to the participant as an infusion, at a flow rate of less than or equal to 2.5 mL/min over ~ 60 minutes.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Vials of BMS-986237 injection must be stored at 2° to 8°C (36° to 46°F) protected from light and it must not be frozen. Further instructions for dilution and infusion of BMS-986237 injection are provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between BMS-986237 and polyvinyl chloride (PVC) and polyolefin containers/IV components have been observed.

7.2 Method of Treatment Assignment

All participants will be centrally randomized or using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

Once enrolled in IRT, enrolled subjects that have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for subject randomization:

- Subject number
- Date of birth
- IMDC prognostic score at screening (0 vs 1-2 vs 3-6)

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A or Arm B, stratified by IMDC prognostic score. The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IRT will be detailed in the IRT manual.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

7.3 Blinding

This is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an Interactive Response Technology (IRT). The site will contact the Interactive Response System prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required.

7.4 Dosage Modification

7.4.1 Dose Delay Criteria

Regardless of whether or not the event is attributed to nivolumab, ipilimumab, or BMS-986237, all study treatments must be delayed until treatment can resume. Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Nivolumab, ipilimumab, and BMS-986237 administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
    - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 7.4.3)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.2 Criteria to Resume Treatment

Participants may resume treatment with study treatment when the drug-related AE(s) 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 Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 7.4.3) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis or myocarditis myositis, rhabdomyolysis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.

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

7.4.3 Dose Discontinuation

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. In this instance, the patient would be considered off part 1 of the study and must have a 6 weeks interval before moving on to part 2 of the study (nivolumab monotherapy).

If a participant in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and 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.

Study 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 re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related

uveitis, pneumonitis, bronchospasm, myositis, myocarditis, rhabdomyolysis, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related, diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myositis, myocarditis, rhabdomyolysis, 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 (LFT) abnormality that meets the following criteria requires discontinuation:
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin).
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. However, dosing must be discontinued for any drug related AE that requires treatment with 10mg/day or greater prednisone or equivalent for more than 12 weeks.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

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

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

7.4.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986237 are

considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

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

The above algorithms are found in the Appendix 8 of this protocol.

7.4.5 Treatment of Related Infusion Reactions

Since study treatment contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until

resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate (**for Arm B subjects**) or to 50% of the original infusion rate (**for Arm A subjects**) until completion of the infusion. Monitor participant closely. If symptoms recur, then no further study treatment will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used

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

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

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

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

[redacted]

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and electronic case report form (eCRF).

[redacted]

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study treatment administration in the study are described below. Medications taken within 4 weeks prior to study treatment administration must be recorded on the CRF.

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of the disease under study).

[redacted]

7.7.2 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 are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.3 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 treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

7.8 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 specified in the protocol. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab, ipilimumab, and/or BMS-986237 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

8.1.1 Post Study Treatment Study Follow-up

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

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window. 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.

[redacted]

8.1.3 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[7]

Participants treated with study treatment(s) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD in both Part 1 and Part 2, assessed by the investigator, 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 written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. 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.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule.

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

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

8.2 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.
- As vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.

- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows new or worsening cardiac-related signs, symptoms, or findings (eg, dyspnea at rest/on exertion, heart block, cardiomyopathy or reduced LV function on imaging) consistent with possible cardiac adverse events, the participant should be immediately evaluated to rule out myocarditis toxicity, according to the suspected Myotoxicity (myositis, myocarditis, rhabdomyolysis) adverse event management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

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

Tumor assessment with contrast-enhanced computed tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. Contrast-enhanced CT of the chest, abdomen, pelvis, and other known/suspected sites of disease should be performed for tumor assessments.

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

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

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

CT and MRI scans 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 timepoints.

For participants with known/suspected brain metastasis, a brain MRI without and with contrast (preferred) or a head CT without and with contrast is required at screening to rule out active brain metastasis. Participants with a history of brain metastasis should have surveillance MRI/CT approximately every 12 weeks, or sooner if clinically indicated until disease progression per RECIST 1.1 criteria or treatment discontinuation, whichever occurs later.

Assessments will be performed at baseline and at the timepoints described in Section 2 per RECIST v1.1 criteria (see Appendix 5) until disease progression per RECIST v1.1 criteria (see Appendix 5) or treatment discontinuation, whichever occurs later.

Tumor assessments at other timepoints may be performed if clinically indicated. Assessments of PR and CR must be confirmed at least 4 weeks after initial response. Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST v1.1 criteria. Investigators will also report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria. (See Appendix 5 for specifics of RECIST v1.1 criteria to be utilized in this study.)

For participants who are treated beyond RECIST v1.1 defined progression, assessment will be performed until discontinuation of study treatment (typically triggered when an additional 10% or greater increase in tumor burden volume from the time of initial progression [including all target lesions and new measurable lesions]).

9.1.1 Imaging Assessment for the Study

Central assessments are not planned for this study. However, copies of all scans will be stored at sites for possible future analysis. At the Sponsor's discretion, scans may be collected for possible future analysis if determined to be necessary by BMS at any time.

9.2 Adverse Events

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

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until 100 days after the last dose of study therapy, at the timepoints specified in the Schedule of Activities (Section 2). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

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

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of randomization.

Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

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

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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), **AND**;
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), **AND**;
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

All occurrences of overdose must be reported as SAEs (see Appendix 3).

In the event of an overdose the investigator/treating physician 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. Safety assessments include AEs, physical examinations, vital signs, performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities and Table 9.4.3-1.

Table 9.4.3-1: Laboratory Assessment Panels

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Creatinine Blood Urea Nitrogen (BUN) or Serum Urea Level Glucose	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus

Table 9.4.3-1: Laboratory Assessment Panels

LDH Corrected Calcium	TSH (reflex to free T3 and T4 if abnormal) Lipase Amylase Creatinine clearance (CLcr) - (screening only)
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only)	
Other Analyses	
Pregnancy test (WOCBP only, as described in Section 2).	

9.4.4 Imaging Safety Assessment

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

9.5 Pharmacokinetic

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

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of pharmacokinetic sample collection and processing will be provided to the site in the lab manual.

Serum samples will be analyzed for drug (nivolumab and ipilimumab) and ADA (anti-nivolumab and anti- ipilimumab antibodies) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab.

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

Table 9.5-1: Pharmacokinetic and Immunogenicity Sample Collections (CA209800 Arms A and B)

Part[a]	Study Day[b] (1 Cycle = 3 weeks for Part 1 1 Cycle = 4 Weeks for Part 2)	Time (Event)	Time (Relative to Start of Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
1	C1D1	(Predose)[c]	00:00	X	X	X	X
1	C1D1	(EOI-nivo)[d]	00:60	X			
1	C1D1	(EOI-ipi)[d]	00:60 or 00:30			X	
1	C2D1	(Predose)[c]	00:00	X	X	X	X
1	C2D1	(EOI-nivo)[d]	00:60	X			
1	C2D1	(EOI-ipi)[d]	00:60 or 00:30			X	
1	C4D1	(Predose)[c]	00:00	X	X	X	X
1	C4D1	(EOI-nivo)[d]	00:60	X			
1	C4D1	(EOI-ipi)[d]	00:60 or 00:30			X	
2	C5D1	(predose)	00:00	X	X	X	X
2	CXD1: Every 16 weeks starting with C5D1 (ie, C9D1, C13D1, etc.)	(Predose)	00:00	X	X		
	First 2 Follow-up Visits (Approximately 30 days and up to ~ 100 Days from the Discontinuation of Study treatment)	NA		X	X		

[a] Part 1 indicates first 12 weeks (or 4 cycles) of combination treatment (nivolumab + ipilimumab). Part 2 indicates nivolumab monotherapy period starting from Week 16 (or Cycle 5).

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

[c] Predose: All predose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab or FRC infusion.

[d] EOI-nivo and EOI-ipi PK samples: End of Infusion PK samples for nivolumab and ipilimumab, respectively. **For sequential dosing, EOI samples for nivolumab and ipilimumab should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the 60 minute nivolumab infusion and 30 minutes ipilimumab infusion, respectively. For the FRC dosing, EOI samples for nivolumab and ipilimumab should be collected immediately**

(preferably within 2 - 5 minutes) prior to the end of the 60 min FRC co-infusion. If the end of any infusion is delayed, the collection of the EOI samples should be delayed accordingly.

9.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7 Pharmacogenomics

The final disposition of samples will be conducted per local regulations.

Details on processes for collection and shipment of these samples can be found in Section 9.8.

[redacted]

[redacted]

[redacted]

9.9 Medical Resource Utilization and Health Economics

Evaluating quality of life (QoL) in oncology clinical studies is becoming increasingly important to understand the impact of benefit/risk from the participant perspective. Participant reported outcomes will be captured through the use of three validated self-reported questionnaires: the Functional Assessment of Cancer Therapy-General (FACT-G), the NCCN Functional Assessment of Cancer Therapy- Kidney Symptom Index (FKSI-19) and the EuroQoL Group's EQ-5D (3L version).

The FACT-G is a 27-item questionnaire that measures general cancer health related quality of life. It is one of the most widely used HrQoL cancer specific scales and has been validated in numerous types of cancer participants, across cultures, and in many languages. The scale is a compilation of general questions divided into four primary HrQoL dimensions: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Summary scores can be calculated for each domain in addition to a single overall summary score.

The NCCN FKSI-19 is a 19-item scale that measures tumor specific HrQoL in kidney cancer participants. The FKSI-19 uses five Likert-type response categories that range from "not at all" to "very much". Participants are asked to circle the response category that best characterizes their response over the last 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea and ability to work. General health status will be measured using the EQ-5D.

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

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, etc.) will be collected for all randomized participants. Specifically, healthcare resource utilization is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outparticipant visits, diagnostic tests and procedures, concomitant medications and reasons for the encounters.

Medical resource utilization associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inparticipant and outparticipant)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outparticipant medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)].

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Approximately 102 participants will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 100 treated participants (50 per arm). This number of treated participants was chosen to achieve a sufficient level of precision for estimating the difference in rates of infusion-related reactions between the two treatment arms. Fifty treated participants per arm will allow estimation of the rate difference within 95% confidence limits of ± -20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk. The 20% limit represents what is considered to be a clinically meaningful difference in the rates of infusion-related reactions.

In previously submitted Phase 2/3 studies of nivolumab in combination with ipilimumab (CA209069 and CA209067), AEs in the MedDRA Anaphylactic Reaction SMQ (broad scope) with onset within 2 days after sequential dosing of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg were reported in 24% of treated participants. In the current study, if the observed rate of infusion reactions is equal to 24% among 50 treated participants in each arm, then the 95% CI for the difference in rates of infusion reactions between arms will be (-16.7%, 16.7%).

Table 10.1-1 shows the precision that the sample size of 50 treated participants per arm will provide for estimating infusion reaction rates and rate differences between the treatment arms under different assumed observed rates.

Table 10.1-1: 95% CI for Rates and Rate Differences when Observed in 50 Participants per Arm

Observed AE Rate (95% CI)		Observed Rate Difference (95% CI)
Arm A (Co-administration, FRC)	**Arm B (Sequential administration)**	**Arm A - Arm B**
24% (13.1%, 38.2%)	22% (11.5%, 36.0%)	2% (-14.5%, 18.5%)
24% (13.1%, 38.2%)	24% (13.1%, 38.2%)	0% (-16.7%, 16.7%)
26% (14.6%, 40.3%)	24% (13.1%, 38.2%)	2% (-15.0%, 19.0%)
30% (17.9%, 44.6%)	28% (16.2%, 42.5%)	2% (-15.8%, 19.8%)
30% (17.9%, 44.6%)	30% (17.9%, 44.6%)	0% (-18.0%, 18.0%)

10.2 Populations for Analyses

The first (primary) analysis will be carried out for primary endpoint and safety related secondary endpoints when all participants who are still on-treatment complete Part 1 period. The final analysis will be carried out for efficacy related secondary endpoints when all participants have at least 9 months of follow-up.

Since the primary objective will be addressed by a safety endpoint, the primary endpoint analysis will be based on all treated participants. For consistency, the secondary endpoints will use the same analysis population as the primary endpoint (ie all treated participants).

Population	Description
All Enrolled Participants	All participants who signed an informed consent form and were registered into the IRT.
All Randomized Participants	All participants who were randomized to any treatment group. This is the primary dataset for efficacy listings.
All Treated Participants	All participants who received at least one dose of any study medication. This is the primary dataset for analysis of study conduct, study population, efficacy (including secondary endpoints), exposure, and safety (including primary endpoint).

Population	Description
Pharmacokinetic Participants	All treated participants with available serum time-concentration data.
Immunogenicity Participants	All treated participants with available ADA data.
Biomarker Participants	All treated participants with available biomarker data.

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.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is related to safety and there are no primary efficacy endpoints.
Secondary	One of the secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of participants with a BOR of CR or PR divided by the number of treated participants. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy including radiotherapy, tumor-directed surgery, or systemic anticancer therapy, whichever occurs first. For participants without documented progression or first subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12 following randomization, every 8 weeks for the first 12 months and then every 12 weeks until disease progression. Another secondary endpoint is PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, 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. 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 randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the

Endpoint	Statistical Analysis Methods
	initiation of first subsequent anti-cancer therapy including radiotherapy, tumor-directed surgery, or systemic anticancer therapy. Efficacy related secondary endpoints will be analyzed at the time of final analysis when all participants have at least 9 months of follow-up. Descriptive analyses of secondary efficacy endpoints will be performed. ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each of the treatment arms. BOR will be tabulated for each treatment group. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated using Cochran-Mantel-Haenszel (CMH) methodology, adjusting for the stratification factors IMDC scores at screening. An estimate of the difference in ORRs and corresponding 2-sided 95% CI will be calculated using CMH methodology, adjusting for the same stratification factors as above. PFS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and corresponding two-sided, 95% confidence intervals will be computed. Descriptive HRs and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by IMDC scores at screening. PFS rates at 6 months with 95% CIs will be estimated using KM methodology.
[redacted]	[redacted]

[redacted]	[redacted]
	[redacted]

10.3.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as the number of participants who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated participants. The analysis of the primary endpoint will occur at the time of first (primary) analysis when all participants who are still on-treatment have had at least complete Part 1 period. For the primary analysis, the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after any dose in Part 1 dosing by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals will be reported descriptively. The confidence intervals for the rate estimates will be based on the Clopper and Pearson method. The estimate and confidence interval for the rate difference will be based on CMH method of weighting, adjusting for IMDC scores at screening. Descriptive statistics will be presented using NCI CTCAE v 4.0 by treatment group. Events will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by preferred term.
Secondary	The first secondary endpoint is the incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination period (Part 1). This incidence rate will be defined similarly to the primary endpoint except that the event rate will be based on terms within the narrow scope SMQ rather than the broad scope. The second secondary endpoint is the drug-related Grade 3 - 5 AE incidence rate defined using NCI CTCAE v 4.0 criteria. The drug-related Grade 3 - 5

Endpoint	Statistical Analysis Methods
	AE rate is defined as number of participants who experienced at least 1 AE of Grade 3 or higher, judged to be related to study treatment by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants. The third secondary endpoint is the all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE v 4.0 criteria. The all causality Grade 3 - 5 AE rate is defined as number of participants who experienced at least 1 AE of Grade 3 or higher with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated participants. Safety related secondary endpoints will be analyzed at the time of the first (primary) analysis when all participants who are still on-treatment complete Part 1 period. The first secondary endpoint will be summarized using the same methods as described above for the primary endpoint analysis. The second secondary endpoint, on-treatment drug-related Grade 3 - 5 AEs occurring within 30 days after the last dose of study treatment, will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term by treatment arm. The third secondary endpoint, all causality Grade 3 - 5 AEs, will be summarized using similar methods as described for drug-related Grade 3 - 5 AEs.
[redacted]	[redacted]

For reference, the terms currently included in the MedDRA Anaphylactic Reaction SMQ based on MedDRA version 19.0 are listed in Table 10.3.2-1.

Table 10.3.2-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope
Acute respiratory failure	Broad
Allergic oedema	Broad
Anaphylactic reaction	Narrow
Anaphylactic shock	Narrow
Anaphylactic transfusion reaction	Narrow
Anaphylactoid reaction	Narrow
Anaphylactoid shock	Narrow
Angioedema	Broad
Asthma	Broad
Blood pressure decreased	Broad
Blood pressure diastolic decreased	Broad
Blood pressure systolic decreased	Broad
Bronchial oedema	Broad
Bronchospasm	Broad
Cardiac arrest	Broad
Cardio-respiratory arrest	Broad
Cardio-respiratory distress	Broad
Cardiovascular insufficiency	Broad
Chest discomfort	Broad
Choking	Broad
Choking sensation	Broad
Circulatory collapse	Narrow
Circumoral oedema	Broad
Cough	Broad
Cyanosis	Broad
Dialysis membrane reaction	Narrow
Diastolic hypotension	Broad
Dyspnoea	Broad
Erythema	Broad
Eye oedema	Broad
Eye pruritus	Broad
Eye swelling	Broad
Eyelid oedema	Broad
Face oedema	Broad
Flushing	Broad
Generalised erythema	Broad

Table 10.3.2-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope
Hyperventilation	Broad
Hypotension	Broad
Injection site urticaria	Broad
Irregular breathing	Broad
Kounis syndrome	Narrow
Laryngeal dyspnoea	Broad
Laryngeal oedema	Broad
Laryngospasm	Broad
Laryngotracheal oedema	Broad
Lip oedema	Broad
Lip swelling	Broad
Mouth swelling	Broad
Nasal obstruction	Broad
Nodular rash	Broad
Ocular hyperaemia	Broad
Oedema	Broad
Oedema mouth	Broad
Oropharyngeal spasm	Broad
Oropharyngeal swelling	Broad
Periorbital oedema	Broad
Pruritus	Broad
Pruritus allergic	Broad
Pruritus generalised	Broad
Rash	Broad
Rash erythematous	Broad
Rash generalised	Broad
Rash pruritic	Broad
Respiratory arrest	Broad
Respiratory distress	Broad
Respiratory failure	Broad
Reversible airways obstruction	Broad
Sensation of foreign body	Broad
Shock	Narrow
Shock symptom	Narrow
Skin swelling	Broad
Sneezing	Broad

Table 10.3.2-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope
Stridor	Broad
Swelling	Broad
Swelling face	Broad
Swollen tongue	Broad
Tachypnoea	Broad
Throat tightness	Broad
Tongue oedema	Broad
Tracheal obstruction	Broad
Tracheal oedema	Broad
Type I hypersensitivity	Narrow
Upper airway obstruction	Broad
Urticaria	Broad
Urticaria papular	Broad
Wheezing	Broad

10.3.2.1 Pharmacokinetic Analyses as a Secondary Endpoint

One of the secondary endpoint is to get PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab. PK will be measured using serum concentration-time data.

PK comparisons will be summarized using descriptive summary statistics to compare nivolumab and ipilimumab predose and EOI concentrations administered as FRC to that of sequentially administered nivolumab and ipilimumab.

10.3.2.2 Other Pharmacokinetic Analyses

The nivolumab and ipilimumab concentration vs time data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model, if needed, to compare model based PK parameters and exposure following administration of the FRC and sequential administration. This model will be used to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). If conducted, the results of the population PK analyses will be reported separately.

[redacted]

10.3.2.4 Outcomes Research Analyses

Descriptive summary statistics of Quality of life (QoL) assessments will be presented at baseline and each on-study time point, unless otherwise specified. Mean changes from baseline for each of the three scales will be calculated for each subject at each on-study time point. In addition, subject compliance will be described per time point by the proportion of subjects who filled out the QoL assessments over the numbers of subject known to be alive and eligible for assessment at these time points.

10.3.2.5 Other Analyses

Methodology for other analyses including pharmacogenomics, immunogenicity, and healthcare resource utilization is described in the statistical analysis plan finalized before database lock.

10.3.2.6 Interim Analyses

Not applicable.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride

Term	Definition
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FRC	Fixed Ratio Combination
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate

Term	Definition
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg^{++}	magnesium
min	minute

Term	Definition
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MS	mass spectrometry
MTD	maximum tolerated dose
μg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
UV	ultraviolet

Term	Definition
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the 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:

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

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

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., 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 for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on-site.

It is however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

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:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design

- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

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

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 drug and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

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: o 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) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 8.1.1 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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 drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[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] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and 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)

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 for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT 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 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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, 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.

2 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).

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 nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 RESPONSE CRITERIA

3.1 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.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 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.

3.1.1.2 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 (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.

3.1.1.3 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'.

3.2 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 and normalization of tumor marker level. 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) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

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

3.2.1.1 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 (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. 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.

3.2.1.2 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 a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols 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.

3.2.2 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.

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.

If a new lesion is equivocal, for example because of its small size, continued therapy and 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.

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. 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.

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 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 3.3.2-2 is to be used.

Table 3.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 3.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

3.3.3 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 later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

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 3.3.3-1: Best Overall Response (Confirmation of CR&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[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration [b]met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

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

[b] Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than

28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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.

APPENDIX 6 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80%
Time from diagnosis to treatment < 1 year
Laboratory
Hemoglobin < LLN
Corrected calcium > ULN
Absolute neutrophil count > ULN
Platelet count > ULN

LLN = Lower limit of normal
ULN = Upper limit of normal

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Group**
0	Favorable
1-2	Intermediate
3-6	Poor

Reference: Heng D, Xie W, Regan M, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009; 27(34):5794-5799.

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	
Normal activity with effort	80	1	Symptoms, but fully ambulatory
Cares for self. Unable to carry on normal activity or to do active work	70	1	
Requires occasional assistance, but able to care for most of his needs	60	2	Symptomatic, but in bed < 50% of the day
Requires considerable assistance and frequent medical care	50	2	
Disabled. Requires special care and assistance	40	3	Needs to be in bed > 50% of the day, but not bedridden
Severely disabled. Hospitalization indicated though death non imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 8 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

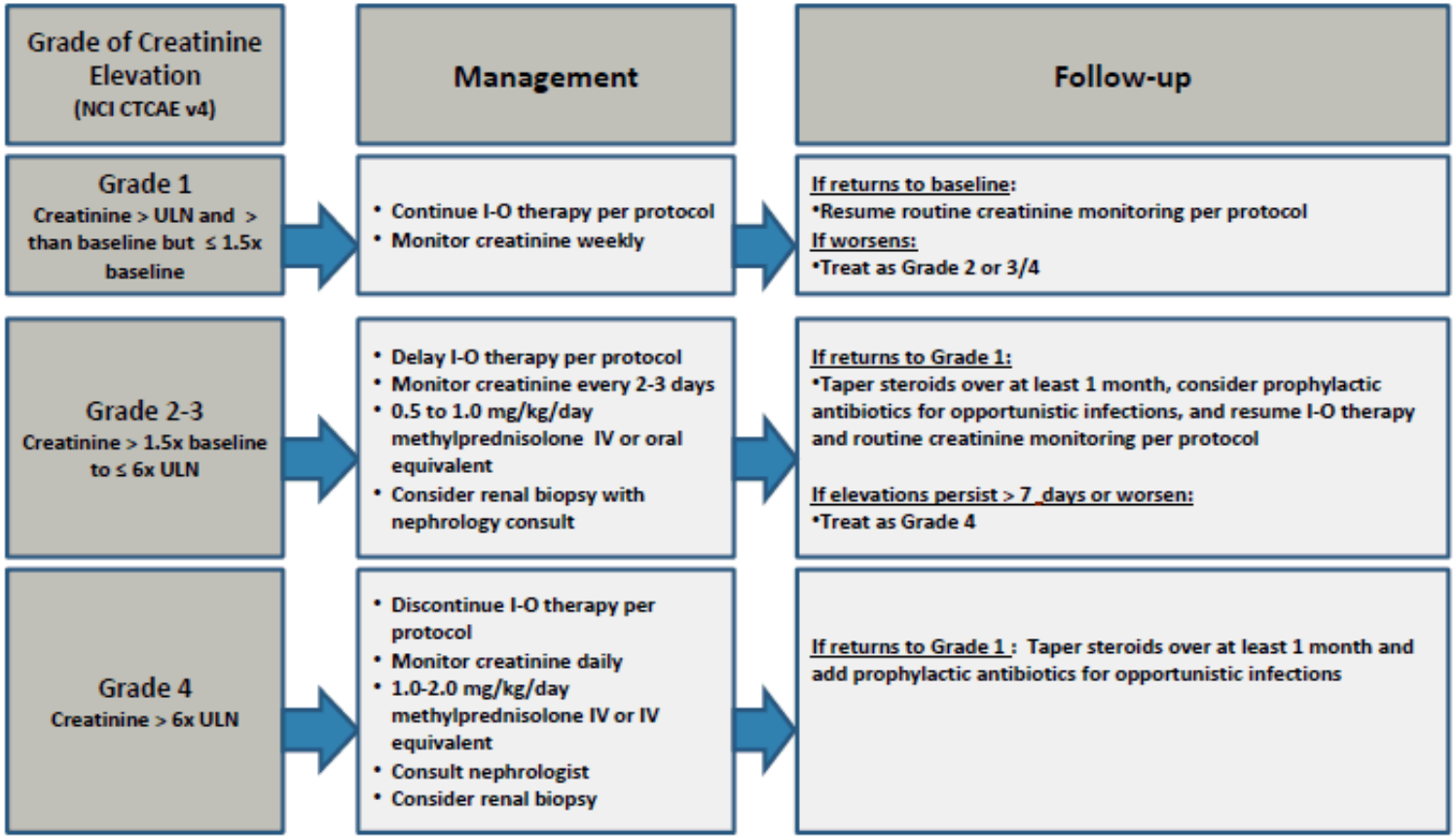
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

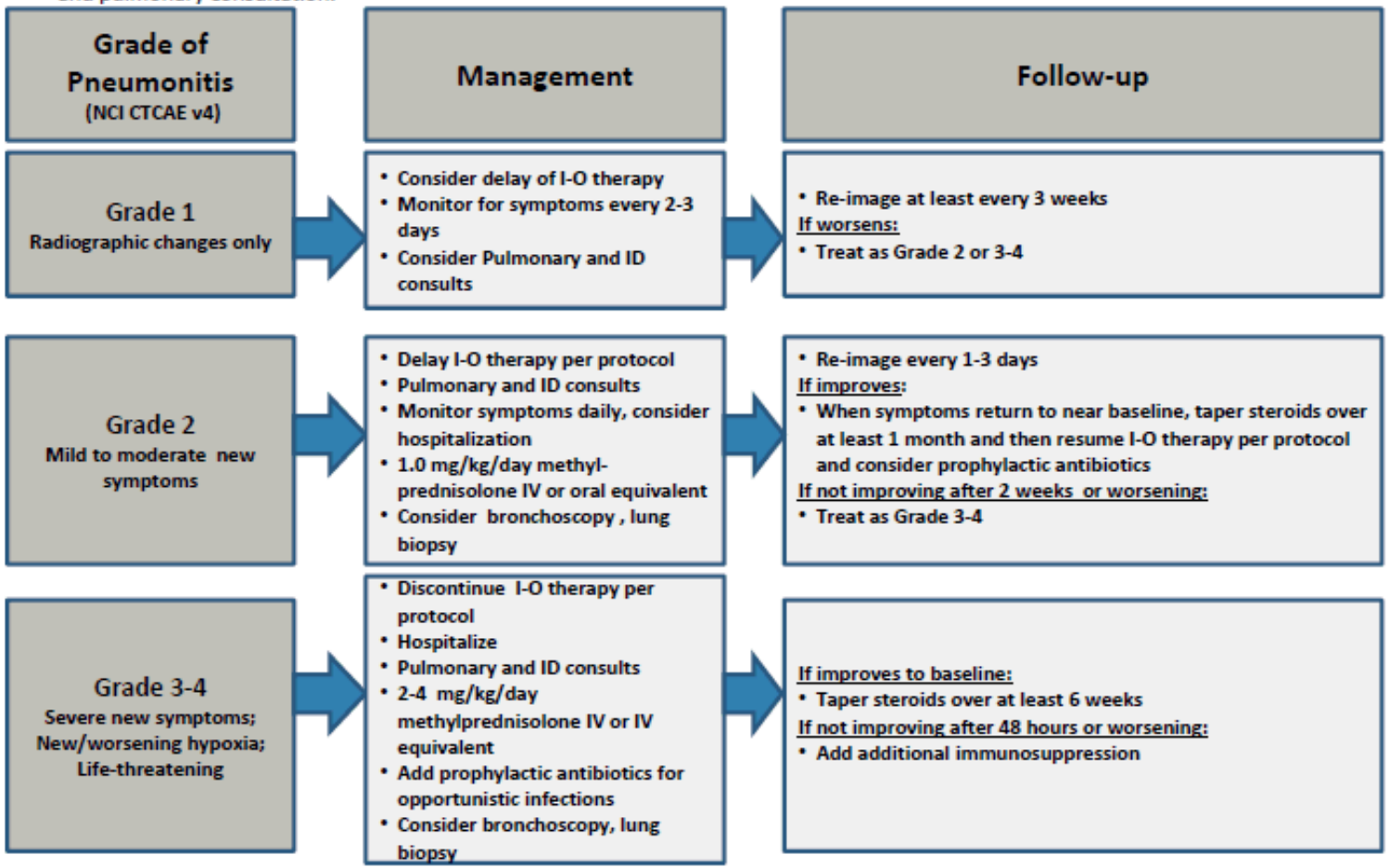


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

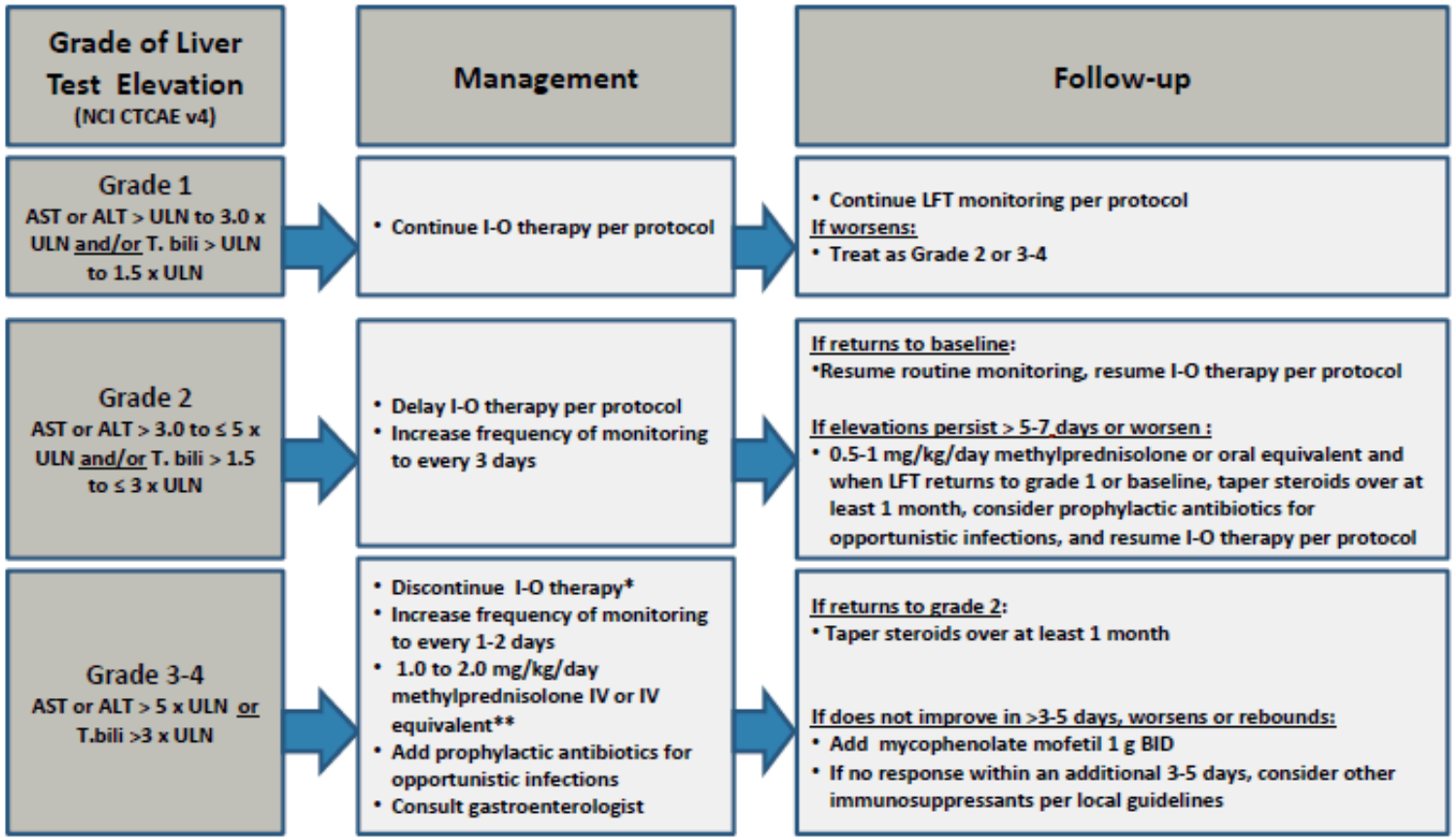


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

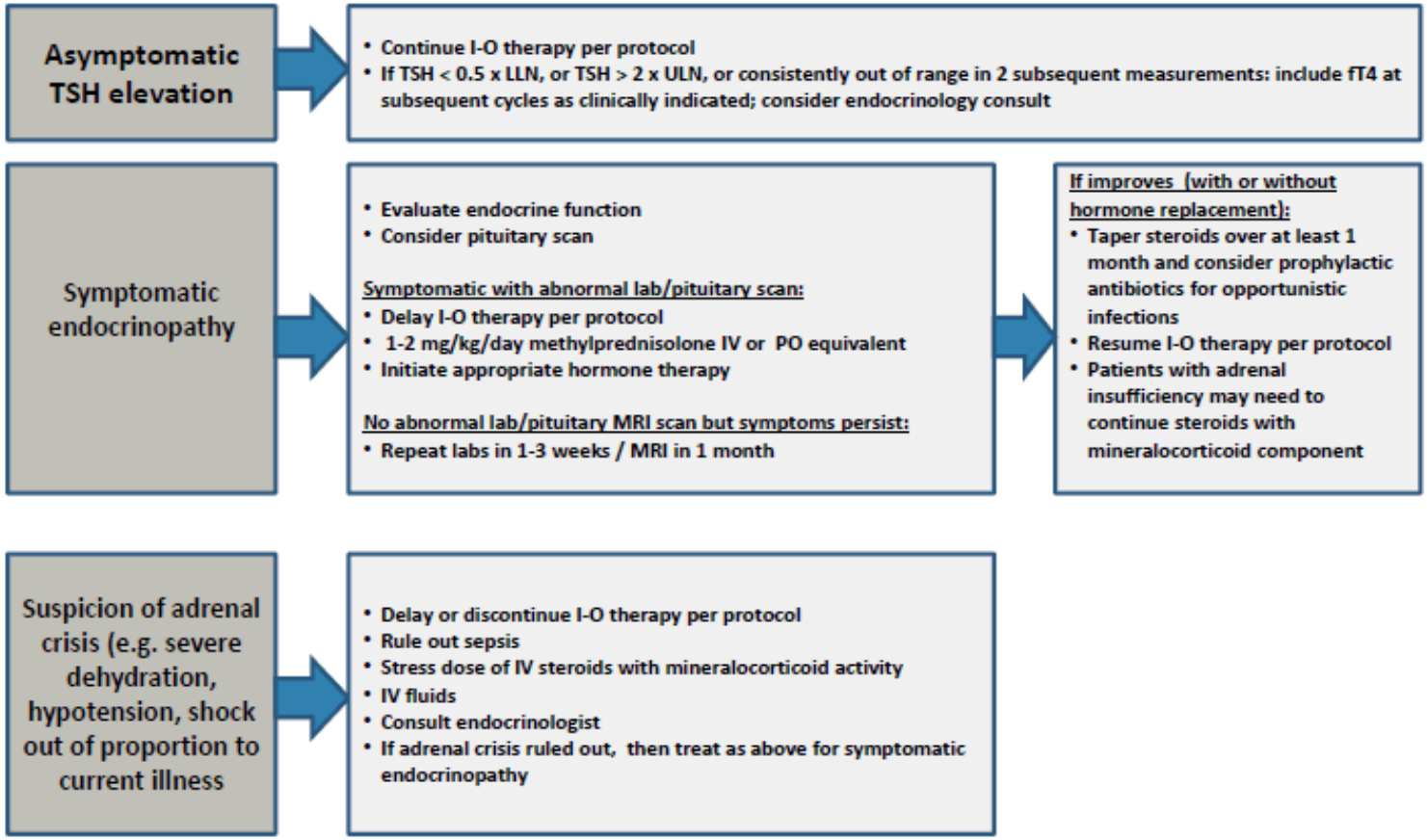
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy 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.

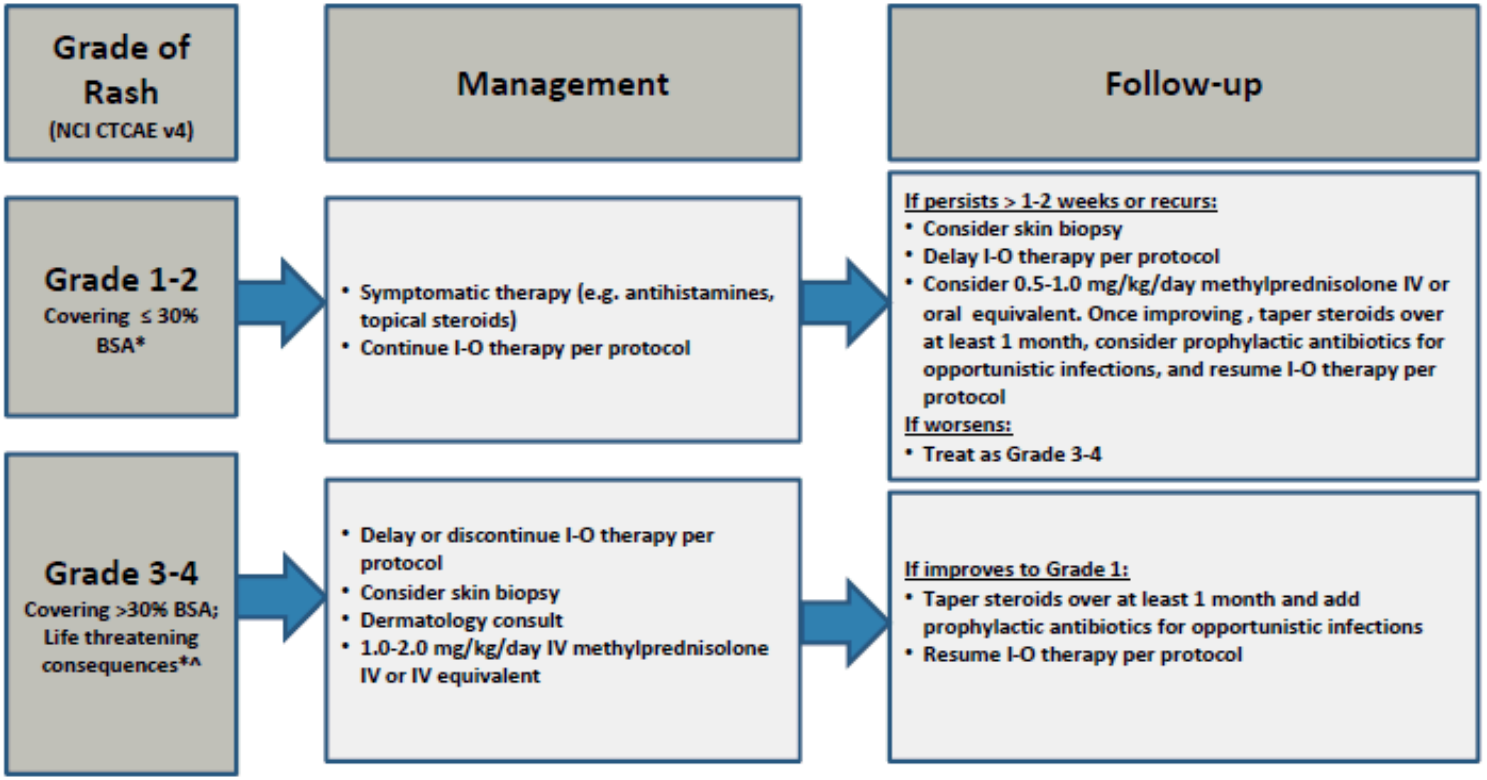


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

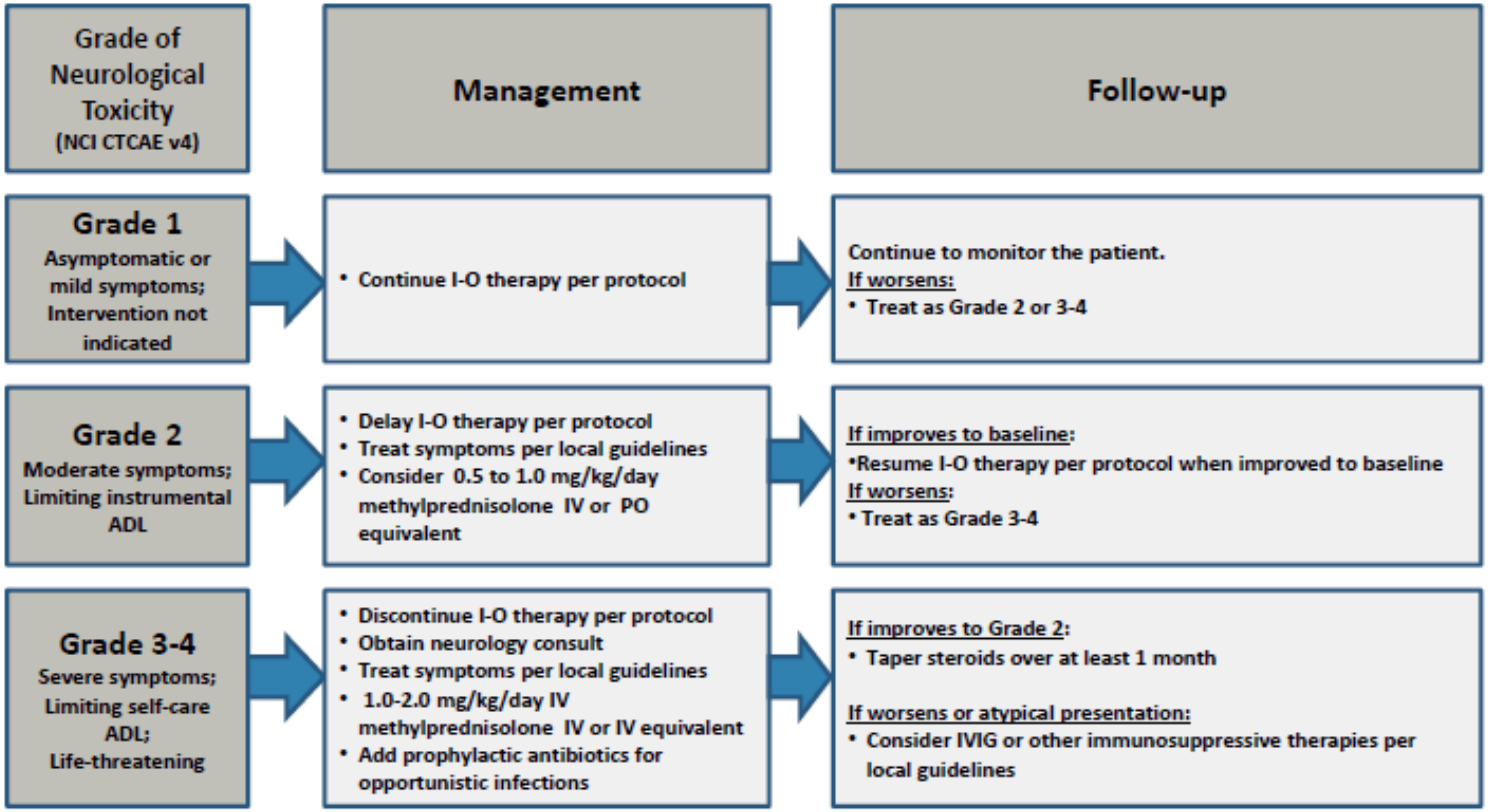


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

Updated 05-Jul-2016

Myotoxicity (Myositis, Myocarditis, Rhabdomyolysis) Adverse Event Management Algorithm

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

Grade of Myotoxicity*	Management	Follow UP
Grade 1: Asymptomatic with laboratory or cardiac imaging abnormalities (myocarditis) Mild pain (myositis)	• Consider delay of I-O therapy • Monitor CPK and troponin and emergence of new symptoms; EKG • Cardiology consultation for abnormal cardiac labs/imaging • Consider steroids (up to 2 mg/kg/day methylprednisolone IV or oral equivalent) • Symptomatic therapy (myositis)	• Close monitoring for new or worsening symptoms • If worsens: Treat as Grade 2 or 3/4

Grade 2:
Symptoms with mild to moderate activity or exertion (myocarditis)
Moderate pain associated with weakness; pain limiting instrumental activities of daily living (myositis)
	• Delay I-O therapy; consider hospitalization
	• Rule out alternative causes (myocardial ischemia, viral infection, nutritional deficiency, thyroid, etc)
	• Prompt cardiology consultation for any cardiac signs and/or symptoms, evaluation may include:
	  • EKG ± continuous cardiac monitoring
	  • Echocardiogram
	  • Troponin and CPK monitoring
	• In absence of cardiac signs and/or symptoms:
	  • Monitor CPK and renal function
	  • Consider EKG and troponin monitoring
	• Up to 2 mg/kg/day methylprednisolone IV or oral equivalent
	• Consider prophylactic antibiotics for opportunistic infections
		• If improves to grade 1 or baseline, taper steroids after cardiac symptoms resolve over at least 1 month
		• Retreatment may be considered after resolution to baseline and completion of steroid taper
		• If no improvement observed, treat as Grade 3-4

Grade 3:
Severe with symptoms at rest or with minimal activity or exertion (myocarditis)
 	
Pain associated with severe weakness; limiting self care activities of daily living (myositis)
 	
Grade 4:
Life Threatening; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy; hospitalize
	• Rule out alternative causes (myocardial ischemia, viral infection, nutritional deficiency, thyroid, etc)
	• Urgent cardiology consultation for any cardiac signs and/or symptoms, evaluation may include:
	  • EKG ± continuous cardiac monitoring
	  • Echocardiogram
	  • Troponin and CPK monitoring
	  • Consider Cardiac MRI and myocardial biopsy
	• In absence of cardiac signs and/or symptoms:
	  • Monitor CPK and renal function
	  • Consider EKG and troponin monitoring
	• 2-4 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Add prophylactic antibiotics for opportunistic infections
		• If improves to grade 1 or baseline, taper steroids over at least 6 weeks
		• If no improvement, consider additional immunosuppressants

*Patients with clinical signs or symptoms of rhabdomyolysis should be evaluated for myositis/myocarditis per the recommendations in this algorithm.