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Clinical Protocol CA025001

A Phase 1 Study of Cabiralizumab (BMS-986227, FPA008) Administered Alone or in Combination with Nivolumab (BMS-936558) in Advanced Malignancies

Revised Protocol Number: 05

Study Director

[redacted]

Medical Monitor
Naoko Murakami

[redacted]

[redacted]

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 05	22-Mar-2018	• Added Clarification in bone marrow sample for efficacy assessments in subject with Multiple Myeloma
Revised Protocol 04	17-Oct-2017	• Removed Survival follow-up after Follow up Period
Revised Protocol 03	12-Sep-2017	• Incorporate DLT criteria with other ongoing studies. • Provided some clarifications in the protocol
Revised Protocol 02	06-Jul-2017	• Added Clarification of the allowance on treatment phase procedural outline • Added Correction and clarification of pharmacokinetic sampling schedule • Provided some clarifications in the protocol
Administrative Letter 01	26-Apr-2017	Clarifications in laboratory test
Revised Protocol 01	08-Mar-2017	Incorporates Amendment 01
Amendment 01	08-Mar-2017	• Added clarification of DLT evaluable participants • [redacted] • Added the clarification of pulse oximetry requiremenet. • Provided some clarifications in the protocol
Original Protocol	17-Jan-2017	Not Applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 05:

The main purpose of this revised protocol is to clarify bone marrow sample for efficacy assessments in subject with Multiple Myeloma in order to reduce ambiguity regarding study procedures:

The revised protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.2.1: Laboratory Assessments	1) Include the detailed explanation regarding FISH 2) Added Minimal Residual Disease (MRD) to Table 9.1.2.1-1	[redacted]
[redacted]		
All	Minor formatting and typographical corrections	

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 1 Study of Cabiralizumab (BMS-986227, FPA008) Administered Alone or in Combination with Nivolumab (BMS-936558) in Advanced Malignancies

Study Phase: 1

[redacted]

Study Population:

Advanced solid tumors and hematologic malignancies who is refractory to or have relapsed after standard therapies, or have no known effective treatment.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess the safety and tolerability of cabiralizumab as monotherapy in subjects with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, death and laboratory abnormalities in monotherapy cohorts.
Secondary	
• To assess the safety of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies.	• Incidence of AEs, SAEs, AEs leading to discontinuation, death and laboratory abnormalities
• To characterize the PK profile of cabiralizumab administered alone and in combination with nivolumab.	• Summary measures of PK parameters (Section 9.5) of cabiralizumab
• To characterize the immunogenicity of cabiralizumab and nivolumab	• Incidence of ADA to cabiralizumab and nivolumab
• To assess the preliminary anti-tumor activity of cabiralizumab administered alone and in combination with nivolumab in subjects with advanced solid tumors.	• BOR, DOR assessed per RECIST 1.1 by investigator
• To assess the preliminary anti-tumor activity of cabiralizumab administered in combination with nivolumab in subjects with hematologic malignancies.	• BOR, DOR assessed per IMWG Response criteria by investigator

Abbreviations: ADA, anti-drug antibody AE, adverse event; DLTs, dose limiting toxicities; BOR, best overall response, DOR, duration of response; PK, pharmacokinetic; SAE, serious adverse event

Overall Design:

This study is a Phase 1, open-label, dose escalation study to evaluate the safety, tolerability, PK, PD and preliminary anti-tumor activity of cabiralizumab as monotherapy in subjects with advanced solid tumor. In addition, the study will evaluate the safety profile, PK, PD and preliminary anti-tumor activity of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies.

For the monotherapy cohorts of the study, cabiralizumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation of toxicity, withdrawal of consent or study closure. For the combination cohorts of the study, cabiralizumab and nivolumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation of toxicity, withdrawal of consent or study closure. Nivolumab will be administered as an IV infusion over 30 minutes, and then cabiralizumab will be administered as an IV infusion over 30 minutes. This study consists of 2 planned cabiralizumab monotherapy cohorts (M1: 2 mg/kg and M2: 4 mg/kg) and 2 cohorts of cabiralizumab in combination with nivolumab (C1: 4 mg/kg cabiralizumab and 3 mg/kg nivolumab in subjects with solid tumor and C2: 4 mg/kg cabiralizumab and 3 mg/kg nivolumab in subjects with hematologic malignancies). The study design schematic is presented in Figure 1 and Figure 2.

Figure 1: Dose Escalation Schema

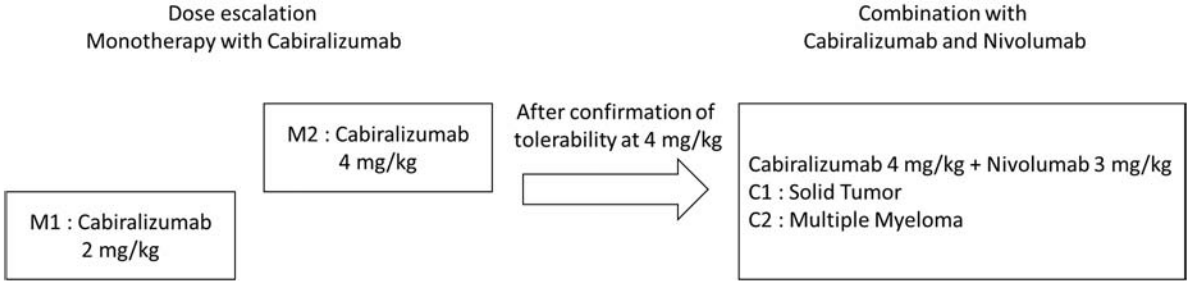
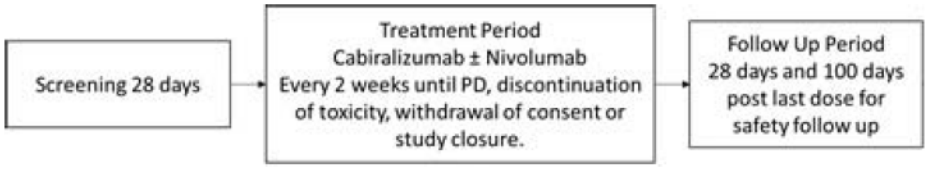


Figure 2. Study Design Schema



A modified Toxicity Probability Interval (mTPI) design will be used to assess the tolerability of cabiralizumab in monotherapy. The DLT evaluation period begins on the first day of treatment and continues for 28 days. Participants who receive at least 2 doses of study drug during the 28-day evaluation interval or participants who discontinue study treatment for drug-related AEs before receiving 2 doses of study drug will be considered evaluable for DLT determination. Dose escalation will be based on the number of DLTs experienced during the DLT evaluation period as determined by the Investigators and Medical Monitor in consultation with Efficacy and Safety Review Committee.

Number of Participants:

This is a Phase 1 study and the sample size cannot be precisely determined and depends on the observed toxicities. Between 6 and 12 subjects are expected to be treated during dose escalation, assuming 2 mg/kg and 4 mg/kg cabiralizumab monotherapy are explored. On the combination cohorts, 6 subjects in each cohort are expected to be treated with 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab following the dose escalation part of monotherapy. In addition, Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each

combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels.

Treatment Arms and Duration:

- Cohort M1: cabiralizumab 2 mg/kg will be administered every 2 weeks until progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.
- Cohort M2: cabiralizumab 4 mg/kg will be administered every 2 weeks until progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.
- Cohort C1/C2: cabiralizumab 4 mg/kg in combination with nivolumab 3 mg/kg will be administered every 2 weeks until progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure.

Study treatment:

Study Drug for CA025001		
Medication	**Potency**	**IP/Non-IP**
Cabiralizumab (BMS-986227) Solution for Injection	100 mg/vial (20 mg/mL)	IP
Nivolumab Solution for Injection	100 mg/vial (10 mg/mL)	IP

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA025001)

Procedure	Screening Visit Within 28 days prior to treatment assignment	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	
Medical History	X	Include any toxicities or allergy related to previous treatments.
Baseline Tumor Assessment	X	
Prior/Concomitant Medications	X	
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 1 day prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height and weight.
ECOG P.S.	X	
Assessment of Signs and Symptoms	X	
Vital Signs	X	Includes body temperature, respiratory rate, and blood pressure and heart rate (sitting or supine). Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Pulse oximetry is performed at rest and after exertion prior to nivolumab dosing at each dosing visit only for the combination cohorts. Refer to Section 9.4.2
Electrocardiogram (ECGs)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.

Table 2-1: Screening Procedural Outline (CA025001)		
Procedure	**Screening Visit Within 28 days prior to treatment assignment**	**Notes**
Laboratory Tests	X	Hematology: CBC with differential, platelets, hemoglobin, hematocrit, RBC Chemistry: CK, AST, ALT, alkaline phosphatase, bilirubin (direct and total), BUN, calcium, chloride, creatinine, glucose, cholinesterase , LDH, phosphorus, potassium, sodium, albumin, amylase, lipase, thyroid panel (TSH, Free T3 and Free T4), PT/INR, PTT (aPTT) and Troponins Urinalysis: Glucose, Protein, Blood
Serology	X	Includes hepatitis C antibody, hepatitis B surface antigen/hepatitis B core antibody, and Interferon-Gamma Release Assays (e.g. Quantiferon test).
Pregnancy Test	X	For WOCBP only.
Follicle Stimulating Hormone (FSH)	X	Women only. Refer to Appendix 4.
Baseline Tumor Assessment		
For Solid tumor : Tumor Assessments	X	Refer to Section 9.1.1
For Multiple Myeloma		Refer to Section 9.1.2
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	X	
Bone Marrow Aspiration/Biopsy	X	Refer to Table 9.1.2.1-1
Skeletal survey	X	
Documentation of extramedullary soft tissue plasmacytomas, if clinically indicated	X	Perform CT or MRI at screening if clinically indicated or if patient had a previous extramedullary or bone plasmacytoma.
[redacted]		
[redacted]	[redacted]	[redacted]

Table 2-1: Screening Procedural Outline (CA025001)		
Procedure	**Screening Visit Within 28 days prior to treatment assignment**	**Notes**
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of participant's written consent

Table 2-2: Treatment Phase Procedural Outline (CA025001)

Procedure	Cycle[a] 1				Cycle 2~	EOT[b]	Follow-up Period	
	D 1	D 2	D 4	D 8	D 1		28 days and 100 days post-last dose	Notes
Safety Assessments								
Physical Examination (PE)	X			X	X	X	X	
ECOG P.S.	X				X	X	X	
Physical Measurements[c]	X				X	X	X	Weight only Within 72 hours prior to dosing.
Vital Signs	X			X	X	X	X	See note in screening procedures and Section 9.4.2. Cohort C1, C2: measure Pulse oximetry at rest and after exertion prior to nivolumab dosing
Electrocardiogram (ECGs) Refer to the DM ECG Study Guidelines	X				C2D1	X		See note in screening procedures and Section 9.4.3 Pre dose and within 1 hour of completion of cabiralizumab dosing on C1D1 and C2D1
Laboratory Tests[c]	X			X	X	X	X	See note in screening procedures and Section 9.4.4. Pre-dose on Day 1 on each cycle. Within 72 hours prior to dosing.
Pregnancy Test[c]	X				X	X	X	Every 2 cycles D1 within 72 hours prior to dosing
Adverse Event Reporting	X							

Table 2-2: Treatment Phase Procedural Outline (CA025001)

Procedure	Cycle[a] 1				Cycle 2~	EOT[b]	Follow-up Period	Notes
	D 1	D 2	D 4	D 8	D 1		28 days and 100 days post-last dose	
Monitor for Non-Serious Adverse Events	X							
Monitor for Serious Adverse Events	X							All SAEs must be collected from the date of participant's written consent until 100 days of discontinuation of dosing
Concomitant Medications Collection	X							
Pharmacokinetic (PK)/ADA Assessments								
Serial Blood PK Sampling	X	X	X	X	X[d]	X	X	See Section 9.5.
ADA sampling	X				X[e]	X	X	See Section 9.5.
[redacted]								
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]					[redacted]			[redacted]
Efficacy Assessments								
Tumor Assessments (for Solid tumor)	X						X[f]	Every 8 weeks (± 7 days) for first 48 weeks, then ever 12 weeks (± 7 days) thereafter See Section 9.1.1
For Multiple Myeloma								

Table 2-2: Treatment Phase Procedural Outline (CA025001)

Procedure	Cycle[a] 1				Cycle 2~	EOT[b]	Follow-up Period	
	D 1	D 2	D 4	D 8	D 1		28 days and 100 days post-last dose	Notes
Myeloma Urine and Serum Lab tests (SPEP/UPEP/sFLC)	X						X[f]	Day 1 on every 2 cycles starting from C3D1
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression							Refer to Table 9.1.2.1-1
Skeletal survey	If clinically indicated							
Documentation of extramedullary soft tissue plasmacytomas, if clinically indicated	As clinically indicated and at the time of CR/sCR assessments							
Flow Cytometry	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression							
Subsequent Treatment (Anti-cancer)							X	
Survival Status							X	
Clinical Drug Supplies								
Study Drug Administration[g]	X				X			Those supplied by BMS

[a] Each cycle is 14-days.

[b] End of treatment (EOT) is defined as the visit where the decision is made to discontinue the participant from treatment.

[c] Physical measurements and laboratory tests do not need to be repeated if completed within the last 72 hours

[d] Cycles 2-9, 13, 21

[e] Cycles 2, 3, 5, 9, 13, 21

[f] Only participants who have not discontinued study treatment for progressive disease.

[g] Every 14 days (2days), subjects may be dosed no less than 12 days from the previous dose.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To assess the safety and tolerability of cabiralizumab as monotherapy in subjects with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, death and laboratory abnormalities in monotherapy cohorts
Secondary • To assess the safety of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies. • To characterize the PK profile of cabiralizumab administered alone and in combination with nivolumab. • To characterize the immunogenicity of cabiralizumab and nivolumab • To assess the preliminary anti-tumor activity of cabiralizumab administered alone and in combination with nivolumab in subjects with advanced solid tumors. • To assess the preliminary anti-tumor activity of cabiralizumab administered in combination with nivolumab in subjects with hematologic malignancies.	• Incidence of AEs, SAEs, AEs leading to discontinuation, death and laboratory abnormalities • Summary measures of PK parameters (Section 9.5) of cabiralizumab • Incidence of ADA to cabiralizumab and nivolumab • BOR, DOR assessed per RECIST 1.1 by investigator • BOR, DOR assessed by IMWG Response criteria by investigator
[redacted]	[redacted]

5 STUDY DESIGN

5.1 Overall Design

This study is a Phase 1, open-label, dose escalation study to evaluate the safety, tolerability, PK, and PD and preliminary anti-tumor activity of cabiralizumab as monotherapy in subjects with advanced solid tumor. In addition, the study will evaluate the safety profile, PK, PD and preliminary anti-tumor activity of cabiralizumab in combination with nivolumab in subjects with advanced solid tumors and hematologic malignancies.

For the monotherapy cohorts of the study, cabiralizumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation of toxicity, withdrawal of consent or study closure. For the combination cohorts of the study, cabiralizumab and nivolumab will be given on Day 1 of each 14-day treatment cycle until the progression of disease, discontinuation of toxicity, withdrawal of consent or study closure. Nivolumab will be administered as an IV infusion over 30 minutes, and then cabiralizumab will be administered as an IV infusion over 30 minutes.

This study consists of 2 planned cabiralizumab monotherapy cohorts (M1: 2 mg/kg and M2: 4 mg/kg) and 2 cohorts of cabiralizumab in combination with nivolumab (C1: 4 mg/kg

cabiralizumab and 3 mg/kg nivolumab in subjects with solid tumor and C2: 4 mg/kg cabiralizumab and 3 mg/kg nivolumab in subjects with hematologic malignancies).

The study will consist of 3 periods: Screening, Treatment and Follow-up. The study will end after the last subject completes the last visit.

Screening begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subjects must have treatment assignment within 28 days after signing the informed consent.

The Treatment Phase begins when the treatment cohort is assigned to the subjects. The subject will be assigned to the open cohort (M1, M2, C1, or C2) at the timing of the treatment assignment. First dose should be started within 3 days of treatment assignment. The subjects will be required to be hospitalized for safety evaluation at least for 8 days from the first dose. The subjects can be discharged at the investigator's discretion at Day 8.

The Follow-Up Phase begins when the decision to discontinue a subject from all treatment is made. Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication. The study design schematic is presented in Figure 5.1-1 and Figure 5.1-2.

Figure 5.1-1: Dose Escalation Schematic

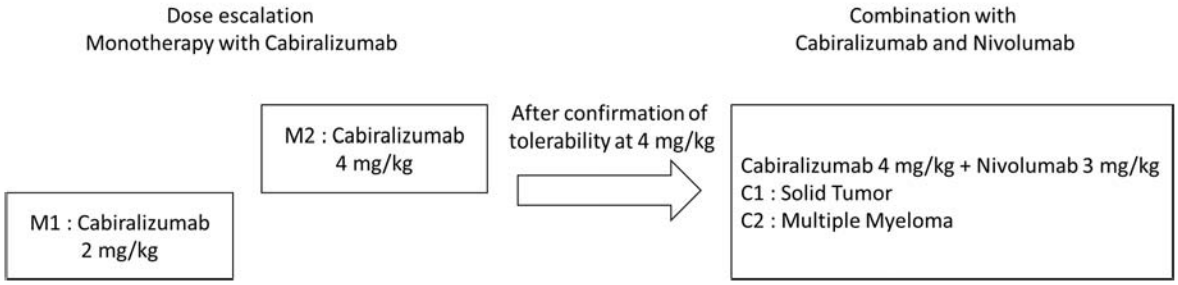
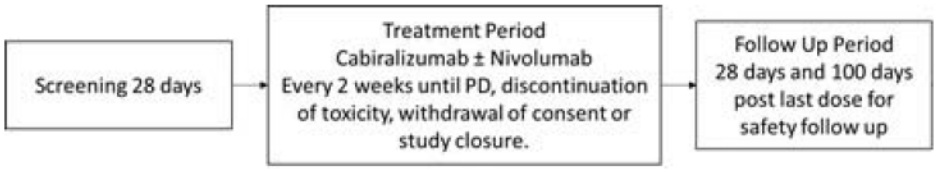


Figure 5.1-2: Study Design Schematic



5.1.1 Cabiralizumab monotherapy dose escalation

Enrollment of subjects in dose escalation part will be guided by the mTPI design. The study design sets a 25% target DLT rate with an equivalence interval of 20 - 30%. Doses of cabiralizumab to be explored in this part of the study will be 2 mg/kg and 4 mg/kg. Decisions regarding dose escalation will be guided by the incidence of DLTs (see Section 5.1.2) occurring within the DLT

evaluation period (28-days) based on the modified Toxicity Probability Interval (mTPI) design. Subjects will be enrolled in successive cohorts of 3 or 6 subjects. The first 3 subjects will receive 2 mg/kg of cabiralizumab every 2 weeks. A decision to proceed to the next higher dose level (4 mg/kg), to add 3 subjects at 2 mg/kg cohort or to stop the enrollment will be made once the first 3 subjects have completed DLT evaluation period. Guided by mTPI, the dose escalation needs to be agreed by the Efficacy and Safety Evaluation Committee after clinical assessment of the totality of available safety data from all treated participants. An additional dose level may also be evaluated if agreed upon by the Investigators, the Sponsor/Medical Monitor and the Efficacy and Safety Evaluation Committee. The performance of the design is reported in Appendix 5. Basically 3 or 6 subjects will be enrolled in a cohort. However, if additional subject will be enrolled in a cohort (e.g. 4 or 7 subjects), dose escalation will be guided by Table 1 in the Appendix 5.

Table 5.1.1-1: Guidance for Dose Escalation/De-escalation Based on Observed Toxicity Outcomes

		Number of Subjects Treated	
		3	6
Number of Subjects with DLTs	0	E	E
	1	S	E
	2	D	S
	3	DU	D
	≥ 4		DU

At Starting dose (2 mg/kg):

E: The current dose level is safe. Escalate and enroll subjects to the next higher dose level (4 mg/kg). If the next higher dose level (4 mg/kg) is deemed to be unacceptably toxic (DU) or has already enrolled 6 or more subjects with D, accept the current dose (2 mg/kg).

S: If 6 or more subjects have already enrolled at this dose level, accept the current dose level (2 mg/kg). Otherwise, stay current dose and enroll 3 additional subjects.

D/DU: The current dose (2 mg/kg) is toxic, stop the enrollment.

At Maximum dose (4 mg/kg):

E: The current dose level is safe. Accept the current dose (4 mg/kg).

S: If 6 or more subjects have already enrolled at this dose level, accept the current dose level (4 mg/kg). Otherwise, stay current dose and enroll 3 additional subjects.

D: De-escalate to the lower dose level (2 mg/kg). Accept the lower dose level (2 mg/kg) if 6 or more subjects have already been enrolled at the lower dose level (2 mg/kg).

DU: The current dose is unacceptably toxic. De-escalate to the lower dose level (2 mg/kg) without re-escalation to the current dose level (4 mg/kg). Accept the lower dose level (2 mg/kg) if 6 or more subjects have already been enrolled at the lower dose level (2 mg/kg).

5.1.1.1 Dose Limiting Toxicity

Non-Hematologic DLT

A DLT is defined as a study drug-related Non-Hematologic ≥ Grade 3 AE (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v 4.0) occurring during the first 28-days, excluding:

- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor),
- Grade 3 rash,
- Grade 3 immune-related adverse event (irAE) that resolved to a Grade 1 or less within 14 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related AE.
- Grade 3 or 4 increase in amylase and/or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
- In the absence of clinical symptoms and other accompanying changes in bilirubin or ALT (as noted in appendices 6, 7and 8), serum elevations of AST/ALT > 12 ×ULN and ≤ 20 ×ULN that last for < 7 days will not be considered a DLT and serum elevations of CK and/or LDH > 15 ×ULN and ≤ 20 ×ULN that last for < 7 days will not be considered a DLT.

Any recurrence of Grade 3 rash, Grade 3 immune-related AE, or Grade 3 infusion-related AE will be considered a DLT. An irAE is defined as a clinically significant AE that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

Definition of Hematologic DLT

Any of the following study drug-related AEs will be considered a hematologic DLT:

- Febrile neutropenia meeting the following criteria: body temperature ≥ 38.3°C at a single measurement, or hyperthermia ≥ 38°C with duration ≥ 1 hour AND neutrophil count < 500/mm^3 or < 1,000/mm^3 and predicted to decrease to < 500/mm^3 within 48 hours
- Grade 4 neutropenia that lasts > 5 days
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 3 or 4 hemolysis
- Hemotoxicities requiring red blood cell or platelet transfusions.

If the events described above or any other clinically significant events occur, these events will be discussed by the investigator, Sponsor/Medical Monitor and the Efficacy and Safety Review Committee to determine whether they qualify as DLT considering its clinical significance.

Participants who receive at least two doses of study drug during the 28-day evaluation interval or participants who discontinue study treatment due to study drug-related AEs before receiving two doses of study drug will be considered as evaluable for DLT determination.

If doses of cabiralizumab are delayed for more than 28 days during the DLT evaluation period because of study drug related AEs, the Investigator and Sponsor/Medical Monitor will consult the Efficacy and Safety Review Committee and decide whether such events should be classified as a DLT or not, and whether subjects with such events should be considered to be "evaluable" or not.

Unevaluable subjects may be replaced at the same dose level. Subjects who miss a dose during the DLT evaluation period may continue on treatment if the subject does not otherwise meet the criteria for permanent discontinuation in Section 8.

Subjects who withdraw from the study during the DLT evaluation period for reasons other than a DLT are not evaluable for DLT and are replaced at the same dose level. The dose escalation to the next dose level and initiation of combination cohort should be determined in consideration of all safety information, including information on adverse events occurred in subjects excluded from DLT evaluation.

5.1.2 Cabiralizumab in Combination with nivolumab:

After tolerability of a dose of 4 mg/kg cabiralizumab monotherapy has been confirmed in the DLT evaluation period of the study, combination cohorts for both subjects with solid tumor and subjects with hematologic malignancies will open in parallel. 6 subjects per each cohort will be enrolled. The start of combination cohorts needs to be agreed by the Efficacy and Safety Evaluation Committee. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to the first doses of cabiralizumab and nivolumab on Day 1 of Cycle 1. Cabiralizumab at a dose of 4 mg/kg and nivolumab at a dose of 3 mg/kg will be administered every 2 weeks.

Sponsor has the option to expand the combination cohorts in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol. Upon completion of 28 days follow-up from the first dose on initial 6 subjects on each combination cohort and after agreed by the Efficacy and Safety Evaluation Committee, up to 24 patients (12 patients with advanced solid tumor and 12 patients with hematologic malignancies) may be enrolled in combination cohorts to fully characterize safety, PK, and PD.

5.1.3 Data Monitoring Committee and Other External Committees

Efficacy and Safety Review Committee will be established in this study.

5.2 Number of Participants

Between 6 and 12 subjects are expected to be treated during dose escalation, assuming 2 mg/kg and 4 mg/kg cabiralizumab monotherapy are explored. On the combination cohorts, 6 subjects each cohort are expected to be treated with 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab following the dose escalation part of monotherapy. In addition, Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol.

5.3 End of Study Definition

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

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

b) Consent for tumor biopsy samples in subjects with solid tumor

i) Subject must consent to allow the acquisition of existing formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides, for performance of correlative studies. An archival sample is acceptable only if there is not systemic immune-oncology therapy administered after the archival sample is collected. If an archived sample is not available, subject must consent to allow a pre-treatment tumor biopsy. In either case, study personnel must ensure that the tissue block or slides physically exist prior to initiating therapy. Subjects unable to provide an archived tumor sample and who either do not consent to a pre-treatment tumor biopsy or do not have accessible lesions are not eligible. Subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone.

ii) Where possible, the biopsied lesion should be distinct from target lesions being evaluated for radiologic response.

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

2) Type of Participant and Target Disease Characteristics

a) Cohort M1, M2 and C1: Subjects must have histologic or cytologic confirmation of an advanced (metastatic and/or unresectable) malignant solid tumor. Primary CNS malignancy is not allowed.

b) Cohort C2: Documented refractory or relapsed multiple myeloma

c) Subjects must be refractory to or have relapsed after standard therapies, or have no known effective treatment. Subjects who refuse or are ineligible for standard therapy will be allowed to enroll provided their refusal/ineligibility is documented in medical records.

d) Subjects cannot have had dose reduced or therapy discontinued due to serious and/or life-threatening IOs-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

   IO: such as, but not limited to, anti-LAG-3, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies

e) Cohort M1, M2 and C1: Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)
   i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

f) Cohort C2: Measurable disease at screening within 28 days of treatment assignment, defined as one or more of the following:
   i) Serum IgG, IgA, or IgM M-protein ≥ 0.5 g/dL
   ii) Urine M-Protein ≥ 200 mg excreted in a 24-hour collection sample
   iii) Involved serum free light chain (sFLC) ≥ 100 mg/L provided the FLC ratio is abnormal

g) Eastern Cooperative Group (ECOG) Performance Status 0-1 (Appendix 9)

h) Cohort M1, M2 and C1: Screening laboratory values must meet the following criteria (using CTCAE v4):
   i) Neutrophils ≥ 1500/uL
   ii) Platelet ≥ $100x10^3$/uL
   iii) Hemoglobin ≥ 9.0 g/dL
   iv) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula)

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

   $$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.0}{72 \times \text{serum creatinine in mg/ dL}}$$

   v) PT/INR ≤ 1.5 x ULN and PTT (aPTT) ≤ 1.5 x ULN
   vi) AST ≤ 3.0 x ULN
   vii) ALT ≤ 3.0 x ULN
   viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)
   ix) Albumin > 3.0 g/dL (pancreatic cancer patients only)

i) Cohort C2: Screening laboratory values must meet the following criteria (using CTCAE v4):
   i) Neutrophils ≥ 750/uL (stable off any growth factor within 2 weeks of first study drug administration)
   ii) Platelet ≥ $50x10^3$/uL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

iii) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 1 week of first study drug administration)

iv) Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 40 mL/min (using the Cockcroft Gault formula)

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

Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.0}{72 \times \text{serum creatinine in mg/ dL}}$

v) PT/INR ≤ 1.5 x ULN and PTT (aPTT) ≤ 1.5 x ULN

vi) AST ≤ 3.0 x ULN

vii) ALT ≤ 3.0 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)

3) Age and Reproductive Status

a) Males and Females, ≥ ages 20

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 1 day prior to the start of study treatment.

c) Women must not be breastfeeding (Even if breastfeeding is suspended, participation in the study is not allowed)

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. 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) Cohort M1, M2, and C1: Untreated or active central nervous system (CNS) or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual

signs or symptoms related to the CNS treatment) for at least 2 weeks prior to treatment assignment. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of <10 mg daily prednisone or prednisone equivalent

b) Cohort M1, M2, and C1: Subjects with hepatocellular carcinoma (HCC)

c) Cohort C2: Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia

d) Cohort C2: Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), amyloidosis, Waldenstrom's macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

e) Cohort C2: Subjects with active plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of plasma/CD138+ cells or an absolute plasma cell count of 2×10^9/L)

f) Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels

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

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

i) Subjects with active or history of interstitial pneumonia or pulmonary fibrosis as diagnosed clinically or by imaging. Patients with radiation pneumonitis will be eligible if stabilization from fibrosis is confirmed and there is no concern for recurrence.

j) Decreased cardiac function with NYHA > Class 2

k) Uncontrolled or significant heart disorder such as unstable angina

l) Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the Investigator, would preclude the patient from exposure to a biologic agent or pose a risk to patient safety

m) Known medical condition 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

n) Evidence of coagulopathy or bleeding diathesis

o) Any major surgery within 4 weeks of study drug administration

p) Participants with a prior malignancy are excluded (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, colorectal, cervical/dysplasia, melanoma, or breast). Participants with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

q) Other active malignancy requiring concurrent intervention

2) Prior/Concomitant Therapy

a) Cohort M1 and M2 (cabiralizumab monotherapy), subjects with prior exposure to anti-CSF1R therapy

b) Cohort C1 and C2 (cabiralizumab and Nivolumab combination therapy), subjects with prior exposure to both of anti-CSF1R therapy and anti-PD-1/PD-L1 antibody as either combination or sequential.

c) Concomitant use of statins while on study. However, a patient using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll

d) Treatment with any anti-cancer therapy or participation in another investigational drug or biologics trial within 28 days prior to first dose of study drug administration

e) Non-oncology vaccine therapies for prevention of infectious diseases (e.g., HPV vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of vaccine.

f) Transfusion completed within 72 hours prior to first dose of study drug administration

g) Cohort C2: Subject has undergone any allogeneic transplant

h) Cohort C2: Subject has undergone autologous transplant within 100 days of initiation of study drugs.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population

b) Significant abnormalities on ECG at screening.

i) QTcF > 450 msec for males

ii) QTcF > 470 msec for females

c) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV-1 and -2 antibody

d) Positive test for latent tuberculosis (TB) at screening [Interferon-Gamma Release Assays (e.g. Quantiferon test)] or evidence of active TB

4) Allergies and Adverse Drug Reaction

a) History of allergy to components of cabiralizumab and/or nivolumab.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

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 (e.g., 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.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment. 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 Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (i.e., participant has not had treatment assignment). If re-enrolled, the participant must be re-consented

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

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

7 TREATMENT

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

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

- Cabiralizumab
- Nivolumab

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

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

Table 7-1: Study treatments for CA025001

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Cabiralizumab (BMS-986227) Solution for Injection	100 mg/vial (20 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab Solution for Injection	100 mg/vial (10 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Cohort	Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
M1[a]	Cabiralizumab	2 mg/kg	Every 2 weeks	Intravenous
M2	Cabiralizumab	4 mg/kg	Every 2 weeks	Intravenous
C1/C2	Cabiralizumab	4 mg/kg	Every 2 weeks	Intravenous
	Nivolumab	3 mg/kg	Every 2 weeks	Intravenous

[a] A lower dose may be tested if appropriate.

Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD subjects enrolled in that dose level may be treated at a lower dose following consultation and agreement between Investigators, the Sponsor and Efficacy and Safety Review Committee.

7.2 Method of Treatment Assignment

All participants will be centrally assigned to treatment. Complete instructions will be provided in a separate manual.

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

Enrolled participants, including those not dosed, will be assigned participant numbers comprised of the site number and subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a participant number of 0001 00101.Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed.

7.3 Blinding

Not applicable.

7.4 Dosage Modification

7.4.1 Dose Delay for Cabiralizumab and Nivolumab

Administration of cabiralizumab and/or nivolumab in combination therapy should be delayed for the following:

- Any Grade 3 fatigue which does not resolve to Grade 1 or baseline before the next treatment visit

- Any drug-related laboratory abnormalities would not require a dose delay unless clinically indicated or specified in the protocol or abnormal laboratory management table (Appendix 8). Please discuss with the Sponsor's Medical Monitor or designee as needed.
- For dose delays or modifications for all other AEs please refer to the AE management tables in Appendix 6 and Appendix 7.

Patients who require a dose delay of cabiralizumab or cabiralizumab/nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume study drug dosing when re-treatment criteria are met. If a patient experiences an infusion reaction to cabiralizumab, or nivolumab, or both study drugs, the infusion reaction should be treated following the infusion reaction treatment guidelines in Section 7.4.5, Appendix 6, and Appendix 7. If the causality of the AE requiring a dose delay is confirmed to be due to one of the study drugs of the combination therapy, the non-offending drug may be continued per protocol taking into account the safety and clinical benefit to the patient.

7.4.2 Criteria to Resume Treatment with Cabiralizumab and Nivolumab

Patients may resume treatment with cabiralizumab and/or nivolumab when the drug-related AE resolves as noted in the AE management tables in Appendix 6 and Appendix 7 or the abnormal laboratory management table in Appendix 8. The Sponsor's Medical Monitor or designee can be contacted at any time if further clarification is needed.

7.4.3 Dose Reduction with Cabiralizumab and Nivolumab

Dose reduction for cabiralizumab and Nivolumab are not permitted.

7.4.4 Treatment beyond Disease Progression with Cabiralizumab and Nivolumab in Subjects with Solid Tumor

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.

Patients treated with cabiralizumab and nivolumab combination therapy will be permitted to continue cabiralizumab and nivolumab treatment beyond initial RECIST v1.1 defined progressive disease, assessed by the Investigator, as long as the following criteria are met:

- Patients who will be treated beyond disease progression must review and sign an ICF before continuing on study drug
- The patient demonstrates investigator-assessed clinical benefit, and do not have rapid disease progression
- Tolerance of study drugs
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

A radiographic assessment/scan should be performed approximately 8 weeks (±7 days) after initial Investigator-assessed progression to determine whether there has been a decrease in the tumor size

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

If the Investigator feels that any patient receiving cabiralizumab and nivolumab will obtain clinical benefit by continuing treatment, the patient may remain on the trial and continue to receive monitoring according to the time and event schedules per protocol.

For the patients who continue cabiralizumab and nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial progression. 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 progression. cabiralizumab and nivolumab treatment should be discontinued permanently upon documentation of further progression.

7.4.5 Treatment of Cabiralizumab and Nivolumab-Related Infusion Reactions

Cabiralizumab and nivolumab may induce infusion or hypersensitivity reactions. If such reactions were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to CTCAE v4 guidelines. Any Grade 3 or Grade 4 infusion reaction should be reported within 24 hours to the Sponsor's Medical Monitor or designee, and reported as an SAE if it meets the criteria.

The nivolumab 30-minute infusion will be administered first, with a 30-minute rest, followed by the cabiralizumab 30-minute infusion. It may be unclear if an infusion reaction is due to cabiralizumab, nivolumab, or to both study drugs. Therefore, one set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study drug) is provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:

For Grade 1 symptoms: Mild reaction (e.g., localized cutaneous reactions including mild pruritus, flushing, rash), requires infusion rate to be decreased; intervention may be indicated.

- Decrease the rate of the study drug infusion until recovery from symptoms.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate.
- If a patient has an infusion reaction with nivolumab, cabiralizumab can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or

paracetamol (acetaminophen) 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction (i.e., any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure >80 mmHg), requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); prophylactic pre-infusion medications indicated for ≤ 24 hours.

- Interrupt the study drug infusion.
- Begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
- Monitor the patient closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms.
- If a patient has an infusion reaction with nivolumab infusion, cabiralizumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- The amount of study drug infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mmHg, or angioedema; Grade 3 symptoms including prolonged symptoms, which require 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae, such as renal impairment, pulmonary infiltrates; Grade 4: life-threatening; pressor or ventilation support indicated.

- Immediately discontinue the study drug infusion. No further study drug will be administered. The amount of study drug infused must be recorded on the CRF.
- Begin an IV infusion of normal saline, and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration,

and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- Remain at bedside and monitor the patient's vital signs until recovery from symptoms.
- The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

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

7.5.1 Dosing of Cabiralizumab and Nivolumab

For patients in the monotherapy cohorts, cabiralizumab infusion will be administered as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle. For the combination therapy, nivolumab should always be administered first as a 30-minute IV infusion followed by a 30-minute infusion of cabiralizumab. The time in between infusions is expected to be approximately 30 minutes but man be more or less depending on the situation. Cabiralizumab ± Nivolumab will be administered every 2 weeks in 14-day (± 2days). Subjects may be dosed no less than 12 days from the previous dose.

Dosing calculations should be based on the body weight assessed at Cycle 1 Day 1 prior to the first dose of study drug administration. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

The calculated dose for Cabiralizumab may be mixed in 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to nominal concentrations of 1.0 mg/mL to 10 mg/mL which can be infused over a period of 30 minutes through an intravenous line containing a sterile 0.22 micron in-line filter. Further guidance and information for the preparation of the study medication is provided in the pharmacy manual.

The calculated dose for Nivolumab may be mixed in 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to nominal concentrations of 1 mg/mL – 10 mg/mL which can be infused over a period of 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding in-line filter. Further guidance and information for the preparation of the study medication is provided in the pharmacy manual.

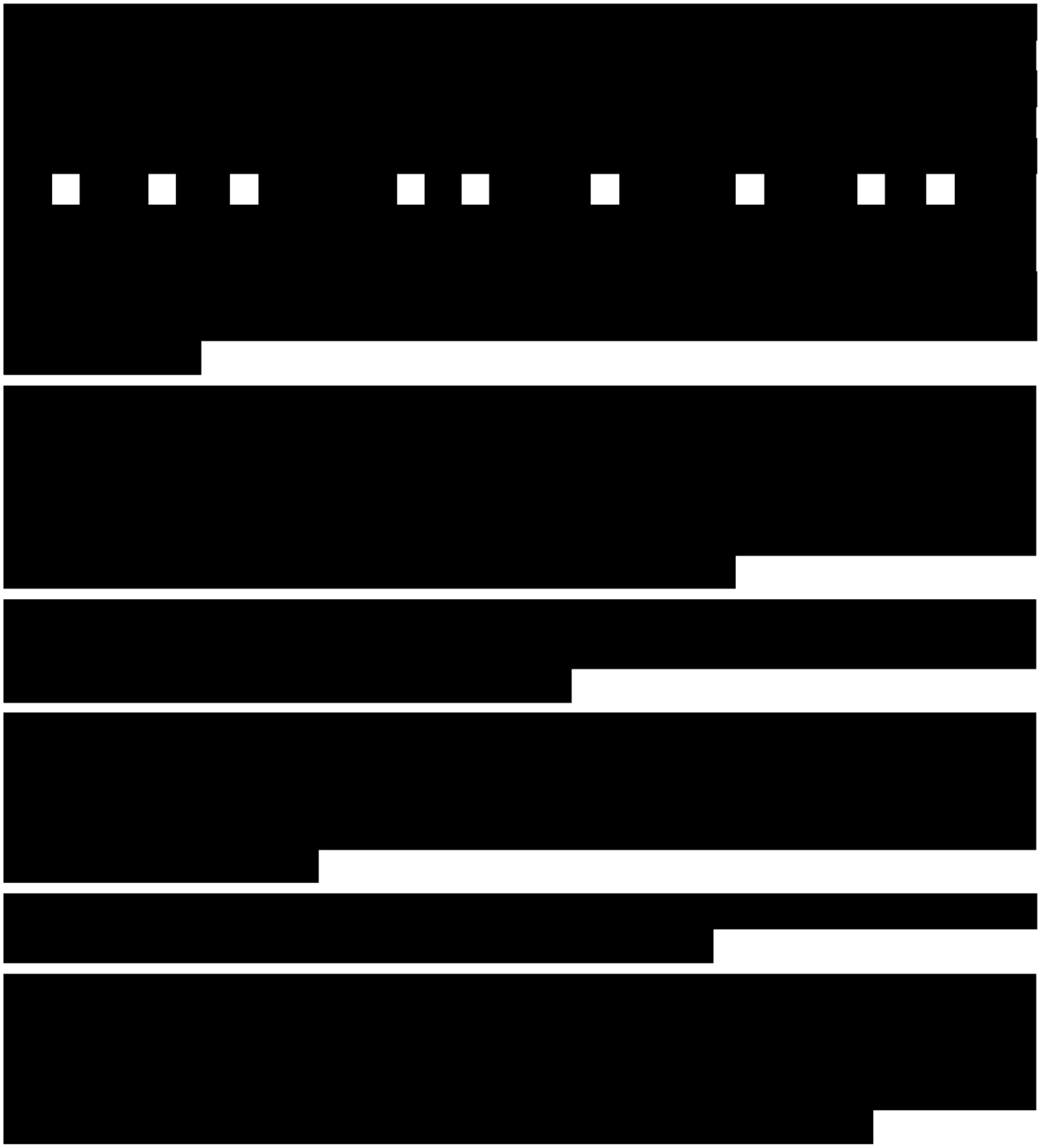
Doses of study drugs may be interrupted, delayed, or discontinued depending on how the patient tolerates the treatment.

7.5.2 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.



7.8 Treatment After the End of the Study

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Documented disease progression or clinical deterioration while receiving active study therapy with exception as described in section 7.4.4.
- Pregnancy
- Patients who are required to have prohibited concomitant medications
- Inability to comply with protocol

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

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 (i.e., 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 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab

Discontinuation rules may be different for monotherapy and combination therapy and not all rules will apply to both arms of the study. For comprehensive discontinuation rules, refer to Appendix 6 (monotherapy) and Appendix 7 (combination therapy) or Appendix 8 (laboratory abnormalities).

Treatment of cabiralizumab in monotherapy or cabiralizumab in combination with nivolumab should be discontinued in the following cases unless otherwise specified:

- Any Grade 3 or higher uveitis ***or*** 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 within the second re-treatment period ***or*** that requires systemic treatment

- Any Grade 3 or higher infusion-related reactions and hypersensitivity requiring discontinuation. Any re-initiation of therapy in this circumstance would require consultation with the Sponsor's Medical Monitor or designee.
- Any Grade 3 non-skin, drug-related AE lasting >7 days, including drug-related uveitis, pneumonitis, hypoxia, bronchospasm, and endocrinopathies with the following exceptions:
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia >7 days or associated with Grade ≥2 bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets any one of the following criteria requires discontinuation:
    - ALT or AST >3x ULN ***and*** total bilirubin >2x ULN ***or*** INR > 1.5 xULN (in the absence of anticoagulation).
        - See Appendix 6 and Appendix 7 for guidelines and possibility of restarting therapy
    - ALT or AST > 20x ULN (with or without concurrent liver metastases)
    - Total bilirubin >3x ULN (>5x ULN with concurrent liver metastases)
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia <7 days
    - Grade 4 lymphopenia or leukopenia <7 days
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor's Medical Monitor or designee should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor's Medical Monitor or designee.
    - Grade 4 CK up to 20 xULN (in the absence of clinical sequelae)
- Any event that leads to delay in dosing lasting >6 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting >6 weeks from the previous dose, the Sponsor's Medical Monitor or designee 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 per protocol, or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.
    - Dosing delays lasting >6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor's Medical Monitor or designee.

Prior to re-initiating treatment in a patient with a dosing delay lasting >6 weeks, the Sponsor's Medical Monitor must be consulted. Tumor assessments should continue per protocol every 8 weeks (±7 days) even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per-protocol or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.

- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, presents a substantial clinical risk to the patient with continued cabiralizumab and/or nivolumab dosing
- Any Grade 3 or higher neurological toxicity
- Any Grade 3 or higher periorbital edema and persistent Grade 2 periorbital edema requiring 2 missed doses unless approved by Sponsor's Medical Monitor
- Any Grade 3 or higher drug-related diarrhea or colitis, which does not resolve to Grade 1 or baseline within 28 days.
- Any Grade 4 skin toxicity
- Any Grade 4 renal toxicity
- Any Grade 3 or higher pulmonary toxicity
- If the causality of the adverse event requiring discontinuation is confirmed to be due to one of the study drugs in the combination therapy, the other drug may be continued per protocol schedule under the following scenarios:
    - Timely resolution of the adverse event based on the treatment modification table
    - Clinical benefit is shown by the patient based on Investigator assessment

8.1.2 Post Study Treatment Study Follow-up

In this study, safety and tolerability information 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 for at least 100 days after the last dose of study therapy.

8.2 Discontinuation from the Study

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

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

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- 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 treatment assignment. 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 (e.g., 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.

9.1 Efficacy Assessments

BOR and DOR per RECIST 1.1 (Appendix 10) or IMWG Response criteria (Appendix 11) by investigator evaluation per each participants will be assessed for efficacy.

9.1.1 Efficacy Assessment in Subjects with Solid Tumor

9.1.1.1 Imaging Assessment

Tumor assessments will be performed at Screening (within 28 days prior to first dose), then every 8 weeks (± 7 days) from the first dose, for the first 12 months, and then every 12 weeks (± 7 days) thereafter. All patients should have tumor response parameters assessed at the End-of-Treatment visit unless a tumor assessment has been performed within 8 weeks prior to an End-of-Treatment Visit or if tumor progression was previously determined. Patients who enter Long-Term Follow-up while showing clinical benefit should have tumor assessments every 12 weeks (± 7 days) for duration of response. The same measuring modality should be preferably used by the site to maintain consistency across the study.

Response will be evaluated using RECIST v1.1 for measurable disease. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. These assessments will follow the same schedule as the radiological assessments.

At the sponsor's discretion, scans may be collected for review.

Contrast enhanced CT with PO/IV contrast or contrast enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

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

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

may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Screening assessments are to be perform performed within 28 days prior to treatment assignment. In addition to the chest, abdomen, pelvis, and brain (to rule out brain metastases), all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease using the same imaging method and technique as was used at baseline.

In addition, subjects receiving cabiralizumab and nivolumab treatment beyond progression must continue tumor assessments until such treatment has been discontinued. Treatment beyond Disease Progression with Cabiralizumab and Nivolumab in Subjects with Solid Tumor is reported in 7.4.4.

9.1.2 Efficacy Assessments in Subjects with Multiple Myeloma

9.1.2.1 Laboratory Assessments

All efficacy laboratory assessments (SPEP, UPEP, serum/urine immunofixation, and sFLC) and bone marrow assessment will be done locally. M protein absolute quantification (eg, g/dL or g/L) or sFLC (eg, mg/L or mg/dL) must be performed. Any laboratory samples analyzed locally be entered on the appropriate CRF/eCRF as requested by the Sponsor to properly assess efficacy per protocol criteria.

1) Serum: SPEP for M protein quantification, total serum protein, serum immunofixation, and quantitative immunoglobulin assay
   a) Serum Immunofixation (IFE) is required at screening and to confirm CR regardless of whether measurable M-protein was present at screening.
   b) Subjects with measurable disease in SPEP will be assessed for response based on SPEP and not by the serum FLC assay.
   c) Subjects with measurable disease in both SPEP and UPEP will be assessed for response based on these two tests and not by the serum FLC assay.
   d) Subjects with FLC only disease should be monitored by sFLC only; SPEP, UPEP and IFE are required only to code CR in those subjects
2) Serum free light chain (sFLC)
   a) Subjects without measurable serum M-protein (ie, < 0.5 g/dL (5 g/L)) or urine M-protein (ie, < 200 mg (0.2 g) per 24 hours) and considered oligosecretory must have sFLC assessed at every 2 cycles starting from C3D1.
   b) Serum for sFLC analysis must be collected at screening and time of serum and urine IFE negativity to confirm CR. This measurement is required to assess for sCR
3) Urine: 24-hour urine collection for M protein quantification and immunofixation. 24-hour urine must be collected with every 2 cycles starting from C3D1 for all subjects (except FLC only disease subjects).
   a) Urine Immunofixation (IFE) is required at screening and to confirm CR, regardless or whether measurable M-protein was present at screening.
   b) Subjects with measurable disease in UPEP will be assessed for response based on UPEP and not by the serum FLC assay.

c) Subjects with FLC only disease should be monitored by sFLC only; SPEP, UPEP and IFE are required only to code CR in those subjects

4) Bone marrow aspiration/biopsy: percentage of plasma cell

Table 9.1.2.1-1: Bone Marrow Sample

Aspirate	1) Samples required at the following times to evaluate percentage plasma cells: a. Screening (within 28 days of treatment assignment) b. When subject is immunofixation negative in both serum and urine (second bone marrow sample not required for confirmation) i. In addition, evaluate flow cytometry to assess plasma cell clonality (ie, lambda and kappa IHC or flow cytometry to assess light chain restriction. c. At time of suspected disease progression, if needed (see Appendix 11) to assess PD in subjects whose myeloma become nonsecretory. Evaluation of percentage of plasma cells should be performed locally per institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed of bone marrow core biopsy. 2) Genetic assessments (FISH) should be performed on a fresh bone marrow sample locally at screening (within 28 days of treatment assignment), which may include but are not limited to: t(4 ;14), t(14 ;16), and del(17p). 3) Samples should be collected and sent to the central lab at the following times to evaluate Minimal Residual Disease (MRD) status at times of potential CR. a. Screening (within 28 days of treatment assignment) b. At time of confirmation of CR/sCR if applicable
Biopsy	Not required by protocol unless an aspirate sample (at any time point above) is not available due to a dry tap or due to laboratory preferences of the local pathologist

5) Serum Corrected Calcium: Serum corrected calcium should be collected with each cycle for all subjects until disease progression.

Corrected Calcium, mg/dL = (0.8 x [Normal Albumin, g/dL - Subject's Albumin, g/dL] + Serum Ca, mg/dL

9.1.2.2 Skeletal Survey

Skeletal survey, by conventional radiography, for metastatic disease will be performed during 28 days prior to initiation of study drugs. Skeletal survey will be performed on study if clinically indicated (development of compression fracture does not exclude response). Use of conventional or low dose CT scan (ie, of the spine) or MRI bone survey is acceptable. If imaging is performed on treatment for assessment of progression, the site must use the same modality of imaging as used in screening. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. On treatment survey should record whether there is an increase in the number or size of lytic lesions.

9.1.2.3 Assessment of Extramedullary Plasmacytoma

Computed tomography or MRI should be performed at screening, if clinically indicated or if patient had a previous extramedullary or bone plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on study assessments should only be performed if clinically indicated (ie, pain, concern for disease progression), whether or not present at baseline, and at the time of CR/sCR assessment.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at screening. This sum will be used as the reference for on study assessments by which to characterize the objective tumor response.

All documented measurable and non-measurable lesions are to be followed throughout the trial. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment. CT and MRI scanning are the preferable methods of assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less or with cuts of 5 (or 10) mm if spiral CT scanning is used. Imaging-based evaluation is preferred to evaluation by clinical examination. Evaluation by chest x-ray is less preferable than CT or MRI, and should only be used for well-defined lesions surrounded by aerated lung. Clinical examination is only acceptable when lesions are superficial, such as a skin nodule or palpable lymph node. Skin lesions must be documented by a photograph with a ruler. Ultrasound is not acceptable for documentation of measurable disease.

At the sponsor's discretion, scans may be collected for review.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning or MRI. The minimum diameter size should be at least twice the slice thickness.

Non-measurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until within 100 days of discontinuation of dosing, at the timepoints specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

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

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

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

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

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 (as defined in Section 9.2 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 (e.g., 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 (5 months) 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 (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to 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 (e.g., anemia versus low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), or INR > 1.5 xULN (in the absence of anticoagulation)
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

For this study, any dose of cabiralizumab and/or nivolumab greater than the assigned dose, and considered excessive and medically important by the Investigator will be considered an overdose.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities. Standard physical examination will be performed as determined by the Investigator, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow up on AE reports.

9.4.2 Vital signs

Refer to Schedule of Activities. Vital signs include respiratory, heart rate, blood pressure, and temperature in the resting position (sitting or supine). Measure prior to dose and after completion of each IV infusion at the following time points: 10 (±5) minutes, 30 (±10) minutes, and 60 (± 15) minutes, 168 hours (±24 hours) [Cycle 1 only] post cabiralizumab administration; 10 (±5) minutes post nivolumab administration. Pulse oximetry is performed at rest and after exertion prior to nivolumab dosing at each dosing visit only for the combination cohorts.

9.4.3 Electrocardiograms

Refer to Schedule of Activities. 12-lead ECG will be obtained at screening, pre dose and post dose of cabiralizumab (within one hour of completion of cabiralizumab) on C1D1 and C2D1, and end of treatment. If clinically indicated, additional ECGs may be obtained during the study. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- Results of clinical laboratory tests performed at Day 1 on each cycle must be available prior to dosing (unless obtaining assessment results are not possible due to local laboratory feasibility).

Hematology
Hemoglobin
Hematocrit
CBC including differential
Platelet count
RBC

Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Glucose Cholinesterase	Albumin Sodium Potassium Chloride Calcium Phosphorus Creatine kinase Troponins Amylase Lipase TSH FT3, FT4 PT/INR PTT(aPTT)
Urinalysis	
Protein	
Glucose	
Blood	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HBc antibody, and Interferon-Gamma Release Assays (e.g. Quantiferon test) (screening only)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose).	
Follicle stimulating hormone (FSH) (screening only for women only) if required	

If CK elevation is clinically significant, obtain troponins (cardiac), CK isoenzymes, aldolase, and ECG; repeat CK and these additional tests within 48 hours or other interval as clinically indicated, until resolved or stable. If either AST or ALT is elevated, obtain total serum bilirubin, alkaline phosphatase; repeat within 48 hours or other interval, as clinically indicated, until resolved or stable. Additional tests may be obtained at any time, if clinically indicated. If a patient is being followed for a tumor marker (e.g. CA-125, or others), a sample for the tumor marker should be obtained at screening and every other cycle, or if clinically indicated during the study.

9.4.5 Optional Liver Biopsy

Optional liver biopsy may be performed at the discretion of the Investigator with an agreement with the Sponsor in the presence of significant liver enzyme elevations. It is performed to understand whether or not such elevations are clinically/pathologically relevant.

9.4.6 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 and Anti-Drug Antibody (ADA)

Pharmacokinetics of cabiralizumab and nivolumab will be derived from serum concentration versus time data. The pharmacokinetic parameters of cabiralizumab to be assessed, following the intensive PK collection after first dose, are shown in below.

AI_Ctrough	Ctrough Accumulation Index; ratio of Ctrough at steady-state (i.e. Cycle 8) to Ctrough after the first dose
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration after the first dose
AUC(TAU)	Area under the serum concentration-time curve in one dosing interval
Cmax	Maximum observed serum concentration
Ctrough	Trough observed serum concentration (predose at each cycle)
T-HALFeff_Ctrough	Effective elimination half-life that explains the degree of Ctrough accumulation observed
Tmax	Time of maximum observed serum concentration

Individual participant pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic analysis program. Actual times will be used for the analyses.

Table 9.5-1 and Table 9.5-2 are listed the sampling schedule for Cohort M1/M2 and C1/C2 to be the assessment of pharmacokinetics and immunogenicity respectively. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

Additional samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions. The immunogenicity (and corresponding drug exposure) data from these samples will be reported as part of a subject's overall immunogenicity assessment. Uniquely identified specimen collection kits and instructions for collection of "ADA Event Driven" samples will be provided by the central laboratory vendor

Table 9.5-1: Pharmacokinetic Sampling Schedule for Cohort M1 and M2

Study Cycle (Study Day)	Event	Time Hour: Min	Sampling for cabiralizumab	Sampling for ADA (cabiralizumab)
Cycle 1 (Day 1)	Prior to infusion	00:00	X	X
	EOI[a]	00:30	X	
	4 hr post-start of infusion	04:00	X	
Cycle 1 (Day 2)	24 hr post-start of infusion	24:00	X	
Cycle 1 (Day 4)	72 hr post-start of infusion	72:00	X	

Table 9.5-1: Pharmacokinetic Sampling Schedule for Cohort M1 and M2

Study Cycle (Study Day)	Event	Time Hour: Min	Sampling for cabiralizumab	Sampling for ADA (cabiralizumab)
Cycle 1 (Day 8)	168 hr post-start of infusion	168:00	X	
Cycle 2 – 3 (Day 1)	Prior to infusion	00:00	X	X
Cycle 4 (Day 1)	Prior to infusion	00:00	X	
Cycle 5 (Day 1)	Prior to infusion	00:00	X	X
Cycle 6 – 8 (Day 1)	Prior to infusion	00:00	X	
Cycle 9, 13, 21 (Day 1)	Prior to infusion	00:00	X	X
End of Treatment	Post treatment		X	X
Follow-up	-		X	X

[a] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Table 9.5-2: Pharmacokinetic Sampling Schedule for Cohort C1 and C2

Study Cycle (Study Day)	Event (Relative to cabiralizumab)	Time (Relative to start of cabiralizumab infusion) Hour: Min	Sampling for cabiralizumab	Sampling for Nivolumab	Sampling for ADA (cabiralizumab and Nivolumab)
Cycle 1 (Day 1)	Prior to infusion	00:00	X	X	X
	EOI[a]	01:30	X	X	
	4 hr post-start of infusion	04:00	X		
Cycle 1 (Day 2)	24 hr post-start of infusion	24:00	X		
Cycle 1 (Day 4)	72 hr post-start of infusion	72:00	X		
Cycle 1 (Day 8)	168 hr post-start of infusion	168:00	X		

Table 9.5-2: Pharmacokinetic Sampling Schedule for Cohort C1 and C2

Study Cycle (Study Day)	Event (Relative to cabiralizumab)	Time (Relative to start of cabiralizumab infusion) Hour: Min	Sampling for cabiralizumab	Sampling for Nivolumab	Sampling for ADA (cabiralizumab and Nivolumab)
Cycle 2 – 3 (Day 1)	Prior to infusion	00:00	X	X	X
Cycle 4 (Day 1)	Prior to infusion	00:00	X		
Cycle 5 (Day 1)	Prior to infusion	00:00	X	X	X
Cycle 6 – 8 (Day 1)	Prior to infusion	00:00	X		
Cycle 9, 13, 21 (Day 1)	Prior to infusion	00:00	X	X	X
End of Treatment	Post treatment		X	X	X
Follow-up	-		X	X	X

[a] EOI=End of Infusion, This sample should be taken within 15 min after end of infusion for both cabiralizumab and nivolumab.

PK samples will be analyzed for cabiralizumab and nivolumab by validated immunoassays. Immunogenicity samples will be analyzed for anti-cabiralizumab and anti-nivolumab antibodies by validated immunoassays.

Serum samples may be used for potential exploratory bioanalysis (e.g., analysis of drug-ADA immune complexes); exploratory results will not be reported. Serum samples designated for immunogenicity, PK or biomarker assessments from the same collection time point may be used interchangeably, if required (eg, insufficient volume for complete assessment or to follow up on suspected immunogenicity related AE). In addition, serum samples will be archived, if the need arises and to the extent possible.

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9.7 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

This is a Phase 1 safety study and the sample size cannot be precisely determined and depends on the observed toxicities. Between 6 and 12 participants are expected to be treated during dose escalation (Part 1), assuming 2 mg/kg and 4 mg/kg cabiralizumab monotherapy are explored. On the combination cohorts, 6 subjects each cohort are expected to be treated with 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab following the dose escalation part of monotherapy. In addition, Sponsor has the option to expand combination cohorts (up to 12 subjects in total per each combination cohort) at the dose previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Treated	All participants who take at least 1 dose of study treatment.
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least one post baseline immunogenicity assessment
[redacted]	[redacted]

10.3 Statistical Analyses

Part 1 (cabiralizumab monotherapy) and Part 2 (cabiralizumab and nivolumab combination therapy) will be analyzed separately.

The statistical analysis plan will be developed and finalized before database lock.

10.3.1 Efficacy Analyses

The efficacy analyses of best overall response (BOR) will be listed on treated population. Duration of response (DOR) will be listed for participants with a BOR of CR or PR.

Endpoint	Statistical Analysis Methods
BOR BOR for a participant will be assessed per RECIST 1.1 or IMWG by investigator	Listing
DOR DOR for a participant with a BOR of CR or PR or better, is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST 1.1/IMWG or death, whichever occurs first.	Listing

10.3.2 Safety Analyses

All safety analyses will be performed on the Treated population.

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE v4.03.	Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.
Lab abnormalities Laboratory values will be graded according to CTCAE v4.03.	Lab shift table using the worst CTC grade on treatment per participant

10.3.3 Pharmacokinetic Analyses

The following parmacokinetic parameters of cabiralizumab will be summarized.

Endpoint	Statistical Analysis Methods
Cmax, AUC(0-T), AUC(TAU), AI-Ctrough, T-HALFeff_Ctrough	Summary statistics: geometric means and coefficients of variation
Tmax.	Summary statistics: medians and ranges
Ctrough.	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation; plots vs time by dose

PK time-concentration data may be pooled with data from other studies for population PK analysis, which will be presented in a separate report.

10.3.4 Immunogenicity

Endpoint	Statistical Analysis Methods
Incidence of ADA to Cabiralizumab/Nivolumab Baseline ADA-positive subject is defined as a subject who has a ADA detected sample at baseline[a]. ADA-positive subject is a subject with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive subjects and ADA-positive subjects after initiation of the treatment

[a] Baseline sample is the last sample before initiation of the treatment

[redacted]

10.3.6 Other Analyses

Not Applicable.

10.3.7 Interim Analyses

Not Applicable.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
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
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
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

Term	Definition
Ctrough	Trough observed serum concentration
CV	coefficient of variation
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
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

Term	Definition
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K^+	potassium
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
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
PD	pharmacodynamics
PK	pharmacokinetics
PTT	partial thromboplastin time
QC	quality control
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
Subj	subject

Term	Definition
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_Ctrough	Effective elimination half life that explains the degree of Ctrough accumulation observed)
Tmax, TMAX	time of maximum observed concentration
Vss/F (or Vss)	apparent volume of distribution at steady state
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.

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:

- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

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 9.2.7 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.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

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] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[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.*
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

* Not approved in Japan

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 the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- 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 5 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 treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of 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 SIMULATION TO EXAMINE MTPI VS. TRADITIONAL 3+3 FOR DOSE ESCALATION STUDY WITH 2 DOSE LEVELS

The dose escalation part of the study utilizes the mTPI method. The mTPI uses a set of decision rules guided by simple Bayesian models and requires a definition of an equivalence interval (EI), in which any dose is considered close to the true maximum tolerated dose (MTD). For this study, the EI is defined as [20%, 30%] with the target toxicity rate of 25%. With this method, there are 3 intervals in the toxicity probability scale: (0, 20%) that is considered lower than the target toxicity rate, [20, 30%] that is considered within the toxicity target range, and (30, 100%) that is considered toxic.

Using this mTPI design, initially 3 eligible subjects will be treated at the dose level of 2 mg/kg. An additional 3 subjects may be added to the same dose level, and hence a total number of 3 to 6 subjects will be treated for a given dose level. A decision to consider the next higher dose level (4 mg/kg) or stop the enrollment will be guided by the number of subjects with dose-limiting toxicities (DLTs) observed (see Table 1). Basically 3 or 6 subjects will be enrolled in a cohort. However, if additional subject will be enrolled in a cohort (e.g. 4 or 7 subjects), dose escalation will be guided by Table 1.

Table 1: Guidance for Dose Escalation/De-escalation Based on Observed Toxicity Outcomes

		Number of Subjects Treated					
		3	4	5	6	7	8
Number of Subjects with DLTs	0	E	E	E	E	E	E
	1	S	E	E	E	E	E
	2	D	D	S	S	S	S
	3	DU	DU	DU	D	S	S
	4				DU	DU	D
	5						DU
	6						

At Starting dose (2 mg/kg):

E: The current dose level is safe. Escalate and enroll subjects to the next higher dose level (4 mg/kg). If the next higher dose level (4 mg/kg) is deemed to be unacceptably toxic (DU) or has already enrolled 6 or more subjects with D, accept the current dose (2 mg/kg).

S: If 6 or more subjects have already enrolled at this dose level, accept the current dose level (2 mg/kg). Otherwise, stay current dose and enroll 3 additional subjects.

D/DU: The current dose (2 mg/kg) is toxic, stop the enrollment.

At Maximum dose (4 mg/kg):

E: The current dose level is safe. Accept the current dose (4 mg/kg).

S: If 6 or more subjects have already enrolled at this dose level, accept the current dose level (4 mg/kg). Otherwise, stay current dose and enroll 3 additional subjects.

D: De-escalate to the lower dose level (2 mg/kg). Accept the lower dose level (2 mg/kg) if 6 or more subjects have already been enrolled at the lower dose level (2 mg/kg).

DU: The current dose is unacceptably toxic. De-escalate to the lower dose level (2 mg/kg) without re-escalation to the current dose level (4 mg/kg). Accept the lower dose level (2 mg/kg) if 6 or more subjects have already been enrolled at the lower dose level (2 mg/kg).

DU: The current dose is unacceptably toxic. De-escalate to the lower dose level (2 mg/kg) without re-escalation to the current dose level (4 mg/kg). Accept the lower dose level (2 mg/kg) if the maximum of 6 subjects have already been enrolled at the lower dose level (2 mg/kg).

Simulations were conducted to examine the performances of the mTPI design and the traditional escalation A+B designs (including a 3+3 design) for this study. The 3+3 design starts from the lower dose level (2 mg/kg); adapts every cohort of 3 patients; considers the next dose level if unacceptable toxicity rate observed. The "1/3" rule has been used in the designs, in the way that:

- If the observed toxicity rate is < 1/3 in the initial cohort of subjects (3 subjects for the 3+3 design), then this dose level will be considered safe, and proceeding with the next higher dose level will be discussed
- If the observed toxicity rate is < 1/3 in the last cohort of subjects (3 subjects for the 3+3 design), then another 3 subjects will be enrolled to evaluate the safety at a max cohort.
- If the observed toxicity rate is 1/3 in the first cohort of subjects, then another 3 subjects will be enrolled to evaluate this dose level further;
- If the observed toxicity rate is > 1/3 in the first cohort of subjects, then this dose level will be considered too toxic and stop enrollment;
- If the observed toxicity rate is < 1/3 at a max cohort size (6 subjects in total for the 3+3 design), then this dose level will be considered safe and proceeding with the next higher dose level will be discussed;
- If the observed toxicity rate is ≥ 1/3 at a max cohort size (6 subjects in total for the 3+3 design), then this dose level will be considered as too toxic.

The mTPI design is knowledge-driven, which assumes a target toxicity rate. On the contrary, the traditional 3+3 design is algorithm-driven, which uses the "1/3" rule.

Simulation Implementation:

- 10,000 simulated trials
- Target toxicity rate for the mTPI design: 25% with EI = [20, 30%]
- mTPI design as described above
- Traditional 3+3 design as described above

Table 2 Dose-Toxicity Scenarios

Scenario	True DLT Rate	
	2 mg/kg	4 mg/kg
1	0.1	0.15

Table 2 Dose-Toxicity Scenarios

Scenario	True DLT Rate	
	2 mg/kg	4 mg/kg
2	0.1	0.2
3	0.15	0.25
4	0.20	0.25
5	0.25	0.33

Simulation Results:

Simulation results are summarized from all the simulated trials per scenario, and include the following statistics:

- Selected (%): Frequency of each dose level being selected as acceptable dose level.
- DLT rate: The average number of subjects who have DLT across all dose levels.
- Average Sample Size: The average number of subjects across all dose levels.

Table 3 Simulation Results

Scenario	Designs	Items	Selected (%)			DLT Rate	Average Sample Size
			Under 2 mg/kg	2 mg/kg	4 mg/kg		
1		True DLT rate		0.1	0.15		
	mTPI	Selected (%)	3.49	10.74	85.77	12.4	7.6
	3+3	Selected (%)	9.93	19.84	70.23	12.8	9.5
2		True DLT rate		0.1	0.2		
	mTPI	Selected (%)	3.55	15.29	81.16	14.9	8.0
	3+3	Selected (%)	10.16	30.36	59.48	15.3	9.6
3		True DLT rate		0.15	0.25		
	mTPI	Selected (%)	8.19	25.13	66.69	19.6	8.1
	3+3	Selected (%)	20.49	36.15	43.36	19.8	9.3
4		True DLT rate		0.2	0.25		
	mTPI	Selected (%)	14.65	27.50	57.85	22.1	7.7
	3+3	Selected (%)	31.84	30.66	37.50	22.3	8.8
5		True DLT rate		0.25	0.33		
	mTPI	Selected (%)	22.46	37.17	40.36	28.0	7.6
	3+3	Selected (%)	44.17	34.17	21.67	28.0	8.2

In summary, the mTPI design selects the correct dose level more frequently than the traditional 3+3 designs for under the true toxicity rate within EI evaluated. The average toxicity rates for mTPI design are slightly lower than the rates of the traditional designs. The traditional 3+3 designs are more conservative and may select sub-optimal dose frequently.

APPENDIX 6 AE MANAGEMENT FOR CABIRALIZUMAB MONOTHERAPY COHORTS

Hepatic Adverse Event Management without Liver Metastasis		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0 x ULN ***and*** Total bilirubin >2 x ULN **or** INR > 1.5	– Discontinue cabiralizumab therapy per protocol	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non-drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase from baseline. – Notify the Medical Monitor if there is an AST increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT >12 to ≤20 x ULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 2 to ≤ 3 xULN	– Delay cabiralizumab therapy per protocol – Increase frequency of monitoring (including but not limited to) of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia) – Consider imaging to rule out obstruction	**If AST and ALT ≤ 12 xULN for ≤ 28 days:** – Resume routine monitoring – Resume cabiralizumab therapy at same dose level per protocol **If elevations persist at same level for > 28 days or worsen:** – Discontinue cabiralizumab therapy per protocol – Discuss with Medical Monitor
AST or ALT > 20 x ULN ***or*** Total bilirubin >3 x ULN	– Discontinue cabiralizumab therapy	– Continue LFT monitoring per protocol until resolution – Continue monitoring for and other associated clinical signs or symptoms

Hepatic Adverse Event Management with Liver Metastasis		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0 x ULN ***and*** Total bilirubin >2 x ULN **or** INR > 1.5	– Discontinue cabiralizumab therapy per protocol	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever,	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase from baseline. – Notify the Medical Monitor if there is an AST increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT >12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin >3.0 to ≤5 x ULN	– Delay cabiralizumab therapy per protocol – Increase frequency of monitoring (including but not limited to) of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia) – Consider imaging to rule out obstruction	**If AST and ALT ≤ 12 xULN for ≤ 28 days:** – Resume routine monitoring – Resume cabiralizumab therapy at same dose level per protocol **If elevations persist at same level for > 28 days or worsen:** – Discontinue cabiralizumab therapy per protocol Discuss with Medical Monitor
AST or ALT > 20 xULN ***or*** Total bilirubin > 5 xULN	– Discontinue cabiralizumab therapy	– Continue LFT monitoring per protocol until resolution – Continue monitoring for and other associated clinical signs or symptoms

Periorbital Edema Adverse Event Management		
Grade of Periorbital Edema (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1	– Continue dosing cabiralizumab therapy per protocol	**If worsens:** – Follow as stated below
Grade 2	– Delay cabiralizumab therapy per protocol	**If returns to Grade 1 or baseline before the next dosing visit:** – Resume cabiralizumab therapy at same dose level without delay – Routine eye monitoring per protocol, if clinically stable **If swelling persists >14 days but returns back to baseline or Grade 1 within 28 days:** – Continue cabiralizumab therapy upon resolution – If it recurs at Grade 2 or above, discontinue cabiralizumab therapy
Grade ≥3	–Discontinue cabiralizumab therapy per protocol.	**If returns to Grade 1 after discontinuation:** – Follow up until resolution

Infusion Reactions Adverse Event Management		
Grade of Infusion Reactions (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1	– Decrease infusion rate of cabiralizumab therapy per protocol and restart at normal infusion rate once symptoms subside. – Monitor patient and start symptomatic treatment as clinically indicated which includes antihistamines and NSAIDs	**If infusion reaction symptoms subside within 3 hours of cabiralizumab therapy:** – Subsequent dosing should include prophylactic pre-infusion medications for cabiralizumab therapy – Continue cabiralizumab dosing at same level
Grade 2	– Interrupt cabiralizumab infusion – Systemic treatment including NSAIDs, corticosteroids, and antihistamines – Normal saline infusion and constant monitoring of vitals and other parameters – If symptoms resolve, resume infusion at 50% of the infusion rate and then increase to 100% if clinically stable	– Resume cabiralizumab therapy at same dose level – Future dosing with pre-infusion prophylactic medications recommended including antihistamines, NSAIDs, and corticosteroids up to 25 mg as needed **If symptoms recur:** – Discontinue treatment at the visit
Grade ≥3	– Discontinue cabiralizumab therapy per protocol – Follow institutional guidelines for hypersensitivity reaction – Systemic treatment including NSAIDs, corticosteroids and antihistamines – Normal saline infusion and constant monitoring of vitals and other parameters – Bronchodilators as clinically indicated with or without hospitalization	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids, NSAIDs, and antihistamines until resolution as needed – Follow up until resolution

APPENDIX 7 AE MANAGEMENT FOR CABIRALIZUMAB AND NIVOLUMAB COMBINATION THERAPY COHORTS

Gastrointestinal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab 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 v4.03)	**Management**	**Treatment and Follow-Up**
Grade 1: Diarrhea:<4 stools/day over baseline; Colitis: asymptomatic	– Continue cabiralizumab and nivolumab 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 hours; not interfering with ADL; Colitis: abdominal pain; blood in stool	– Delay cabiralizumab and nivolumab per protocol[a] – Symptomatic treatment	**If improves to Grade 1 ≤4 days:** – Resume cabiralizumab and nivolumab therapy per protocol **If persists ≥5–7 days or recurs:** – 0.5–1 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 cabiralizumab and nivolumab therapy per protocol **If worsens or persists >3-5 days with oral steroids:** – Treat as Grade 3 or 4
Grade 3–4: Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; Colitis (G3): Severe abdominal pain, medical intervention indicated, peritoneal signs **Grade 4:** Life-threatening perforation	– Delay or Discontinue cabiralizumab and nivolumab therapy per protocol[b] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Add prophylactic antibiotics for opportunistic infections – Consider lower endoscopy if clinically indicated	**If Grade 3 AE improves to Grade 1 or baseline within 28 days:** – Taper steroids over at least 1 month – Resume dosing of cabiralizumab and Nivolumab **If Grade 4:** – Permanently discontinue cabiralizumab and Nivolumab – Continue steroids until Grade 1, then taper steroids over at least 1 month **If persists >3-5 days, or recurs after improvement:** – Add infliximab 5 mg/kg (if no contraindications) – Follow up until resolution – Note: Infliximab should not be used in cases of perforation or sepsis

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient

[c] 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.

Renal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Creatinine Elevation (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1: Creatinine >1.0x to 1.5x baseline; >1 x ULN to 1.5x ULN	– Continue cabiralizumab and nivolumab therapy at the same dose level per protocol – Monitor creatinine weekly	**If returns to baseline :** – Resume routine creatinine monitoring per protocol **If worsens:** – Follow as stated below
Grade 2: Creatinine >1.5x to 3.0x baseline; >1.5 x ULN to 3.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[c] – Consider renal biopsy if clinically indicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist >14 days or worsen:** – Treat as Grade 4
Grade 3: Creatinine >3.0 x baseline; >3.0x ULN to 6.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[c] – Consider renal biopsy if clinically indicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist > 14 days or worsen:** – Treat as Grade 4
Grade 4: Creatinine >6.0x ULN	– Discontinue cabiralizumab and nivolumab therapy per protocol [b] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consult nephrologist – Consider renal biopsy if clinically indicated	**If returns to baseline or Grade 1:** – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections **If worsens:** – Follow up until resolution – Clinical referrals as needed

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Pulmonary Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Evaluate with imaging and pulmonary consultation.		
Grade of Pneumonitis (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1: Radiographic changes only	– Consider delay of cabiralizumab and nivolumab therapy – Monitor for symptoms every 2 to 3 days – Consider pulmonary and infectious disease consults	– Re-image at least every 3 weeks **If worsens:** – Treat as Grade 2 or 3–4
Grade 2: Mild to moderate new symptoms	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Pulmonary and infectious disease consults – Monitor symptoms daily, consider hospitalization – 1 mg/kg/day methylprednisolone IV or oral equivalent – Consider bronchoscopy, lung biopsy, if clinically indicated	– Re-image every 1–3 days **If improves <14 days:** – When symptoms return to near baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy per protocol **If does not improve after 2 weeks or worsens:** – Treat as Grade 3–4
Grade 3–4: Severe new symptoms; New/worsening hypoxia; Life-threatening	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Hospitalization – Pulmonary and infectious disease consults – 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent[c] – Add prophylactic antibiotics for opportunistic infections – Consider bronchoscopy, lung biopsy if clinically indicated	**If improves to baseline:** – Taper steroids over at least 6 weeks **If does not improve after 48 hours or worsens:** – Add additional immunosuppression (e.g. cyclophosphamide, IVIG, or mycophenolate mofetil) – Follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Hepatic Adverse Event Management without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Medical Monitor if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 2 to ≤ 3 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN – If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately	**If AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring – Resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but ≤ 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level. – Consider tapering steroids over at least 1 month **If elevations persist at the same level > 28 days or worsen:** – Discontinue cabiralizumab and nivolumab therapy per protocol – 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Medical Monitor

Hepatic Adverse Event Management without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
	– Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	
AST or ALT > 20 xULN ***or*** Total bilirubin >3 xULN	– Discontinue cabiralizumab and nivolumab therapy[b] – Increase frequency of monitoring to every 1 to 2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab therapy per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Medical Monitor if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 3.0 to ≤ 5 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN	**If AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but ≤ 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:**

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
	– If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Discontinue cabiralizumab and nivolumab therapy per protocol – 0.5–1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Medical Monitor
AST or ALT > 20 xULN ***or*** Total Bilirubin > 5 xULN	– Discontinue cabiralizumab and nivolumab therapy[b] – Increase frequency of monitoring to every 1–2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2 or baseline:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Endocrinopathy Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider visual field testing, endocrinology consultation, and imaging.		
Description	**Management**	**Follow-Up**
Asymptomatic TSH elevation	– Continue cabiralizumab and nivolumab therapy per protocol	**If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements:** – Include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult
Symptomatic endocrinopathy	– Evaluate endocrine function – Consider pituitary scan **Symptomatic with abnormal lab/pituitary scan:** – Delay cabiralizumab and nivolumab therapy per protocol[a] – 1 to 2 mg/kg/day methylprednisolone IV or PO equivalent[c] – Initiate appropriate hormone therapy **No abnormal lab/pituitary MRI scan but symptoms persist:** – Repeat labs in 1–3 weeks and MRI in 1 month	**If improves within 28 days (with or without hormone replacement):** – Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapy per protocol – Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component **If persists for over 28 days:** – Delay cabiralizumab and nivolumab therapy – Continue steroids as needed – Upon resolution, discuss with Medical Monitor if patients are clinically stable on further dose delay and discontinuation – Follow up until resolution or return to baseline
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Rule out sepsis – Stress dose of IV steroids with mineralocorticoid activity – IV fluids – Consult endocrinologist – crisis is ruled out, treat as above for symptomatic endocrinopathy	

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Skin Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Rash (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1–2: Covering ≤30% BSA[d]	– Symptomatic therapy (e.g. antihistamines, topical steroids) – Continue cabiralizumab and nivolumab therapy per protocol	**If persists >1-2 weeks or recurs:** – Consider skin biopsy – Delay cabiralizumab and nivolumab therapy per protocol – Consider 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. – Once improving ,taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy per protocol **If worsens:** – Treat as Grade 3–4
Grade 3–4: Covering >30% BSA; Life-threatening consequences[d]	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Consider skin biopsy and dermatology consult – 1 to 2 mg/kg/day IV methylprednisolone IV or IV equivalent[c]	**If improves to Grade 1 within 28 days:** – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapy per protocol **If persists > 28 days or worsens:** –Consider to discontinue cabiralizumab and nivolumab therapy per protocol

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient

[c] 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.

[d] Refer to NCI CTCAE v 4.03 for term-specific grading criteria.

Neurological Adverse Event Management		
Grade of Neurological Toxicity (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1: Asymptomatic or mild symptoms; Intervention not indicated	– Continue cabiralizumab and nivolumab therapy per protocol	**If worsens:** – Treat as Grade 2, 3, or 4
Grade 2: Moderate symptoms; Limiting instrumental ADL	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Treat symptoms per local guidelines – Consider 0.5 to 1 mg/kg/day[c] methylprednisolone IV or PO	**If improves to baseline within 28 days:** – Resume cabiralizumab and nivolumab therapy at same dose level per protocol when improved to baseline **If worsens or persists after 28 days:** – Treat as Grade 3-4
Grade 3–4: Severe symptoms; limiting self-care ADL; life-threatening	– Discontinue cabiralizumab and nivolumab therapy[b] – Obtain neurology consult – Treat symptoms per local guidelines 1 to 2 mg/kg/day IV methylprednisolone or PO[c] – Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** – Taper steroids over at least 1 month **If worsens or atypical presentation:** – Consider IVIG or other immunosuppressive therapies per local guidelines – Continue follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Periorbital Edema Adverse Event Management		
Grade of Periorbital Edema (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Periorbital Edema > baseline but **< Grade 2**	– Continue cabiralizumab and nivolumab therapy per protocol – Monitor edema weekly	**If worsens:** – Follow as stated below
Grade 2	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Start systemic treatment including steroids, eye drops, or analgesics as needed[c]	**If returns to Grade 1 or baseline before the next dosing visit:** – Continue systemic treatment – Resume cabiralizumab and nivolumab therapy at same dose level without delay – Routine eye monitoring per protocol, if clinically stable **If swelling persists >14 days but returns back to baseline or normal within 28 days:** – Continue nivolumab and cabiralizumab dosing at same level – If recurs at Grade 2 or above, discontinue cabiralizumab and nivolumab therapy
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Systemic treatment including steroids, eye drops, or analgesics as needed[c] – Consult Ophthalmologist if needed	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids as needed – Any follow up and ophthalmology consults, if clinically indicated – Monitor and follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

[c] 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.

Infusion Reaction Adverse Event Management		
Grade of Infusion Reactions (NCI CTCAE v 4.03)	**Management**	**Follow-Up**
Grade 1	– Decrease infusion rate of cabiralizumab and nivolumab therapy per protocol and restart at normal infusion rate once symptoms subside – Monitor patient and use symptomatic treatment as clinically indicated (which includes antihistamines and NSAIDs)	**If infusion reaction symptoms subside within 3 hours of nivolumab** – cabiralizumab therapy can be given without any prophylactic medications if the reaction is nivolumab related – Subsequent dosing should include prophylactic pre-infusion medications for nivolumab – If the infusion reaction is related to cabiralizumab therapy, prophylactic medication should be given prior to dosing of cabiralizumab and nivolumab – Continue cabiralizumab and nivolumab dosing at same level
Grade 2	– Interrupt cabiralizumab and/or nivolumab infusion per protocol[a,b] – Systemic treatment including NSAIDs, corticosteroids and antihistamines[c] – Normal saline infusion and constant monitoring of vitals and other parameters – If symptoms resolve within 3 hours, continue infusion at 50% rate for 30 minutes and then increase to 100% if clinically stable	– Resume cabiralizumab and nivolumab therapy at same dose level and monitor per protocol – Pre-infusion prophylactic medications are recommended for future dosing, including antihistamines, NSAID and corticosteroids up to 25 mg as needed. **If symptoms recur:** – Discontinue treatment at the visit – Discuss with Medical Monitor as needed
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Systemic treatment including NSAID , corticosteroids and antihistamines[c] – Normal saline infusion and constant monitoring of vitals and other parameters – Follow institutional guidelines for anaphylaxis – Bronchodilators as clinically indicated with or without hospitalization	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids, NSAIDs, antihistamines until resolution, as needed – Follow up until resolution – Any other clinical referrals, if indicated

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient

[c] 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.

Uveitis Adverse Event Management		
Grade of Uveitis (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1	– Observe symptoms – Continue cabiralizumab and nivolumab therapy	– Watch for worsening of symptoms including visual disturbances, light sensitivity, decrease vision – Monitor weekly **If worsens:** – Follow as stated below
Grade 2	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Start antibiotics and inflammatory medications including steroids[c] – Ophthalmologic consult, if clinically indicated – Immunosuppressive agents (e.g, anti-TNF agents such as Infliximab)	**If symptoms resolve within 14 days:** – Continue cabiralizumab and nivolumab therapy at same dose level and start tapering of steroid doses **If symptoms resolve between 14 -28 days:** – Consider continuing dosing at same dose level for nivolumab and a dose level lower for cabiralizumab on resolution to baseline or Grade 1 and start tapering of steroid doses. – If it is Grade 2 drug related uveitis which does not resolve within 14 days, consider to discontinue study drug(s) **If symptoms persist or worsen in 28 days regardless of systemic treatment:** – Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such as infliximab, as clinically indicated
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Start antibiotics and inflammatory medications including steroids[c] – Ophthalmologic consult, if clinically indicated – Immunosuppressive agents (e.g, anti-TNF agents such as Infliximab)	– Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such as infliximab, as clinically indicated – Follow up until resolution

[a] If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient

[b] If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient

[c] 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.

APPENDIX 8 LABORATORY ABNORMALITIES MANAGEMENT TABLE

Laboratory Abnormalities Management (CK and LDH)		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
CK > 10 xULN	– Consider measuring CK isoenzymes as clinically indicated	**If CK isoenzymes are abnormal** – Consider checking troponin levels – Consider other assessments (including uromyoglobin) as clinically indicated **If CK isoenzymes are normal** – Continue dosing, per protocol – Monitor CK level as clinically indicated
CK or LDH > 15 to ≤ 20 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Measure CK isoenzyme panel to identify source of elevation – Increase frequency of monitoring (every 48-72 hours, or more, as clinically indicated) – Notify the Medical Monitor	**If returns to ≤ 15 xULN within ≤ 28 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol – If CK isoenzyme panel is normal continue monitoring the subject. – If CK isoenzyme panel is abnormal then consider measuring troponins. – If troponins are abnormal, contact Medical Monitor to determine if the subject can be retreated. **If elevations persist at the same level > 28 days or worsen:** – Discontinue further dosing – Discuss with Medical Monitor
CK or LDH > 20 xULN	– Discontinue cabiralizumab and nivolumab therapy	– Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

APPENDIX 9 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS [a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

a [redacted]

APPENDIX 10 RESPONSE CRITERIA (RECIST 1.1)

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 < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, 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 11 DEFINITIONS OF RESPONSE AND PROGRESSION CRITERIA (MODIFIED FROM IMWG)

Response Subcategory	Response Criteria[a]
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio[b] and absence of clonal cells[c] in bone marrow by immunohistochemistry or immunofluorescence.
Complete Response (CR)[b]	Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)[b]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein level plus urine M-protein level < 100 mg per 24 hour.
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. If serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minor (Minimal) Response (MR)	25-49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50-89%, which still exceeds 200 mg per 24 hours. In addition, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression.

Response Subcategory	Response Criteria[a]
Progressive disease	Any of the following: 1. Increase of 25% from lowest response value in any one or more of the following: a. Serum M-component (absolute increase must be ≥ 0.5 g/dL (5g/L))[d] and/or b. Urine M-component (absolute increase must be ≥ 200 mg (0.2g) per 24 h) and/or c. Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL (100mg/L)) d. Bone marrow plasma cell percentage (absolute % must be ≥ 10%) 2. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas 3. Development of hypercalcemia (corrected serum calcium > 11.5 mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder

[a] All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[b] Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved FLC levels.

[c] Presence or absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] For progressive disease, serum M-component increase of ≥ 1 g/dL (10g/L) is sufficient to define progression if starting M-component is ≥ 5 g/dL (50 g/L).

APPENDIX 12 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 03, 12-Sep-2017

The main purpose of this revised protocol is to incorporate DLT criteria with other ongoing studies. In addition, administrative changes are incorporated in the revised protocol.

The revised protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
Section2: SCHEDULE OF ACTIVITIES Table 2-1 Table 2-2	Notes of Physical Examination (PE) and Tumor Biopsy (for solid tumor) were modified from 24hours to 1day.	
Section2: SCHEDULE OF ACTIVITIES Table 2-2 Section 9.1.1.1: Imaging Assessment 9.1.2.1: Laboratory Assessments	Regarding Follow-up period, Tumor assessment, Myeloma Urine and Serum Lab tests, and Subsequent Treatment in Table 2-2 were updated. The first sentence in the first paragraph of Section 9.1.1.1 and 2)-a. of Section 9.1.2.1 were modified.	
Section2: SCHEDULE OF ACTIVITIES Table 2-2 Section 7.5.1: Dosing of Cabiralizumab and Nivolumab	Study Drug Administration in Table 2-2 and The first paragraph of Section 7.5.1 were modified to add the allowance of Cabiralizumab and Nivolumab dosing.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
Section 3.1.1: Tumor-Associated Macrophages and Colony Stimulating Factor 1 Receptor	The first sentence in the third paragraph was modified to include multiple myeloma.	
Section3.2.1.2 :Clinical Summary Section3.2.3.1 : Serum Enzyme Elevations in Cabiralizumab	Clinical Study and Safety Summary of Cabiralizumab was updated	
Section3.3: Benefit/Risk Assessment	The fifth and sixth paragraph were updated.	
Section 5.1.1.1:Dose-limiting toxicity	The last bullet in Non-Hematologic DLT section was modified.	
Section 7.4.1: Dose Delay for Cabiralizumab and Nivolumab	The last sentence of the last paragraph was added.	
Section 7.4.3: Dose Reduction with Cabiralizumab and Nivolumab	1) The title was modified to include in Nivolumab 2) The sentence was modified not to permit dose reduction for Cabiralizumab	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
Section 8.1: Discontinuation from Study Treatment	1) Add the reasons Participants must discontinue investigational product 2) Deleted the instruction in the case of pregnancy	
Section 9.4.4: Clinical Safety Laboratory Assessments	Delete skeletal from troponin obtained if CK elevation is clinically significant.	
[redacted]		
Appendix 6.7.8	Modified in accordance with the changes in FPA008-003 protocol	
All	Minor formatting and typographical corrections	

Overall Rationale for the Revised Protocol 02, 06-Jul-2017

The main purpose of this revised protocol is to clarify and correct the following points in order to reduce ambiguity regarding study procedures:

- Clarify the allowance for physical measurements and laboratory tests on treatment phase
- Correct and clarify time and event for pharmacokinetic sampling schedule to be collected relative to start of cabiralizumab infusion

In addition, administrative changes are incorporated in the revised protocol.

The revised protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
Section2: SCHEDULE OF ACTIVITIES Table 2-1	1) Laboratory Tests was modified to include Troponin. 2) Documentation of extramedullary soft tissue plasmacytomas was modified to add notes to table.	
Section2: SCHEDULE OF ACTIVITIES Table 2-2	5) Physical Measurements, pregnancy test and Laboratory Tests were modified to include within 72 hours prior in notes and add footnote. 6) Vital signs was modified to add notes to table. 7) EOT was removed from exploratory biomarker assessment	
[redacted]		
Section 6.1: Inclusion Criteria	1)-b)Consent for tumor biopsy samples in subjects with solid tumor was modified	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
Section 6.2: Exclusion Criteria	Exclusion Criteria was modified to include 1)-p) and q).	
Section 7.2: Method of Treatment Assignment	Method of Treatment Assignment was modified to update participant numbers assignment.	
Section 9.1.1.1:Imaging Assessment	11) The first sentence in the first paragraph was modified to include the mention of the end tumor assessment. 12) The last sentence in the last paragraph was added to include the mention of Treatment beyond Disease Progression.	
Section 9.1.2.1: Laboratory Assessments	1) "Baseline" was modified in wording to "screening" 15) Serum free light chain and Urine parts were modified to include "starting from C3D1 to every 2 cycles"	
Section 9.1.2.2: Skeletal Survey	The first sentence in the first paragraph was modified to include "during 28 days prior to initiation of study drugs" in	
Section 9.4.4: Clinical Safety Laboratory Assessments	16) The mention on local laboratory feasibility was added on the third bullet. 17) (APTT) was added to Serum chemistry. 18) Discharge was removed from pregnancy test.	
Section9.5:Pharmacokinetic and Anti-Drug	22) The pharmacokinetic parameters to be assessed was modified to AUC (TAU) from	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
Antibody (ADA) Section10.3.3: :Pharmacokinetic Analyses	AUC (INF), and CLT and Vss were removed. 23) Event, Time and footnote of Table9.5-1 and Table9.5-2 were modified.	
[redacted]		
Section9.6.1: Tumor Tissue Specimens	The second paragraph was modified to include notification to BMS Medical Monitor regarding On-treatment biopsies.	
Section10.2: Population for analyses	Removed the mention of IRT	
Section10.3.4: Immunogenicity	Added Nivolumab to Incidence of ADA	
All	Minor formatting and typographical corrections	

APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 17-Oct-2017

The main purpose of the modification to the CA025001 is to remove Survival follow-up after Follow up Period from the study. Since 1) the number of subjects enrolled in the study will be 36 at a maximum; and 2) enrolled subjects will have various type of cancer, it does not expect survival follow-up to obtain mature data.

Summary of key changes of Revised Protocol 04		[redacted]
Section Number & Title	**Description of Change**	
Section 1: SYNOPSIS Section 2: SCHEDULE OF ACTIVITIES Section 5.1: Overall Design	Figure 2.Study Design Shema has been updated Table 2.2 Treatment Phase Procedural Outline has been updated. Figure 5.1-2 Study Design Shema has been updated.	
Section 8.1.2 Post study Treatment Study Follow-up	The last sentence was modified	
All	Minor formatting and typographical corrections	