Official Title of Study:

A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants with Advanced Renal Cell Carcinoma (FRACTION-RCC)

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Clinical Protocol CA018005

A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants with Advanced Renal Cell Carcinoma (FRACTION-RCC)

Protocol Amendment: 07
Incorporates Administrative Letter 04

[redacted]

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	11-Jan-2022	Given the rapidly evolving treatment landscape in renal cell carcinoma (RCC), having only 1 patient left on safety follow-up, and the complexity and operational challenges faced, the FRACTION-RCC study is planned for closure once the last patient finishes the safety follow-up. The planned termination of the FRACTION-RCC study is not due to any safety concerns. Due to planned early closure of the trial, the study schedule was adjusted to remove retreatment/re-randomization options, response follow-up, and survival follow-up periods for all parts of the study. No changes were made to the treatment period or safety follow-up period.
Administrative Letter 04	02-Nov-2020	Updates to study personnel
Administrative Letter 03	19-Jun-2019	Updates to study personnel
Revised Protocol 06	15-Nov-2018	• Section 2 Schedule of Activities, Table 2-1 Screening Procedural Outline in FRACTION-RCC Cancer Revised Protocol was modified to include clarification of ECG procedure. • Section 4 Objectives and Endpoints was modified to update Tertiary/Exploratory Objective 6 per planned analysis of patient-reported outcomes data. • Section 6.1 Inclusion Criteria were modified to clarify favorable risk profile and Karnofsky Performance Status requirements. • Section 7.7.1 Prohibited and/or Restricted Treatments was modified to include language clarifying marijuana use. • Section 9.1 Efficacy Assessments was edited to provide language consistent with Table 2-1 and clarify collection of details of progressive disease in relation to participant's prior therapy. • Paragraphs describing activities related to patient-reported outcomes were moved to Section 9.1.2 Patient-reported Outcomes. • Other key changes include updates made to safety guidance and/or reporting activities to align the protocol with current policies and safety parameters, in the following sections: Section 9.2.5 Pregnancy; Section 9.3 Overdose; Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting; Appendix 4, Contraception Guidance for Female Participants of Child Bearing Potential; and Appendix 6 Hepatic Adverse Event Management Algorithm.
Administrative Letter 02	20-Jun-2018	Updated study personnel
Revised Protocol 05	27-Apr-2018	• Synopsis was revised to reflect the changes in the protocol body and is now included under section 1 in revised protocol 05. • Exclusion criteria in FRACTION-RCC Cancer Revised Protocol were added to exclude favorable risk patients who have not have been treated with sunitinib prior to randomization into Track 1 for treatment with nivolumab plus ipilimumab.

Document	Date of Issue	Summary of Change
		• The Schedule of Activities Table was revised to include collection of risk information as defined by International Metastatic RCC Database Consortium (IMDC) score (detailed language provided in Appendix 8), as well as testing for Methemoglobin level and Glucose-6-phosphate Dehydrogenase Deficiency. • Incorporates Appendix 8 International Metastatic RCC Database Consortium (IMDC) Prognostic Criteria. • Statistical considerations includes an updated description for enrollment of the participants. • The trial design and sample size determination were modified to allow for enrollment to continue until efficacy evaluation complete.
Revised Protocol 04	08-Feb-2018	• Revised to allow participants to continue treatment for up to a total duration of 2 years.
Revised Protocol 03	15-Jun-2017	Incorporates Amendment 03
Amendment 03	15-Jun-2017	• Change of Study Director/Medical Monitor, Restoration of inadvertently deleted neutrophil inclusion criterion and clarification of hemoglobin inclusion criterion
Administrative Letter 01	25-Apr 2017	• Correction of wording concerning Hepatitis C antibody testing in Table 2-1 and Table 2-2 and wording concerning Hepatitis A antibody testing in Table 9.4.1-1.
Revised Protocol 02	01-Mar-2017	Incorporates Amendment 02
Amendment 02	01-Mar-2017	• Removal of Legally Authorized Representitive language, Clarification of Inclusion Criteria, updates to the procedural outline
Revised Protocol 01	28-Sep-2016	Incorporates Amendment 01
Amendment 01	28-Sep-2016	• Clarification of the overall study design
Original Protocol	23-Aug-2016	Not Applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

Given the rapidly evolving treatment landscape in renal cell carcinoma (RCC), having only 1 patient left on safety follow-up, and the complexity and operational challenges faced, the FRACTION-RCC study is planned for closure once the last patient finishes the safety follow-up. The planned termination of the FRACTION-RCC study is not due to any safety concerns. Due to planned early closure of the trial, the study schedule was adjusted to remove retreatment/re-randomization options, response follow-up, and survival follow-up periods for all parts of the study. No changes were made to the treatment period or safety follow-up period.

Sections in the synopsis have been updated to align with the protocol section changes listed below. In addition, this Protocol Amendment 07 incorporates changes from approved Administrative Letter 04, which do not appear in the table below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07

Section Number & Title	Description of Change	Brief Rationale
Table 2-2, Baseline for Re-randomization Procedural Outline	Added "Not applicable per Protocol Amendment 07" in the title.	This change was made to clarify the removal of re-randomization option.
Table 2-3, Follow-up Procedural Outline	Footnote "b" marked as "Not applicable per Protocol Amendment 07." Added footnote "c" for clarification.	These changes were made to clarify the removal of the re-treatment/re-randomization option, Response Follow-up, and Survival Follow-up periods for the study.
Section 3.3, Benefit/Risk Assessment	Added language on the risk assessment of non-live coronavirus disease 2019 (COVID-19) vaccination.	This change was made to address unknown effects of newly available COVID-19 vaccines.
Section 5.1.1, FRACTION-RCC Tracks 1 and 2 Design; Section 5.1.3, Study Phases	Updated language in these sections (including footnotes for Figure 5.1.1-1) for removal of re-treatment/ re-randomization, Response Follow-up, and Survival Follow-up related description.	These changes were made to clarify the removal of the re-treatment/re-randomization option, Response Follow-up, and Survival Follow-up periods for the study.
Section 7.4.2, Treatment Beyond Disease Progression	Updated with "Not applicable per Protocol Amendment 07."	This change was made to clarify the removal of the option for treatment beyond progression.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.3, Permitted Therapy	Added text permitting non-live COVID-19 vaccination.	This change was made to adopt the BMS guidance allowing the use of COVID-19 vaccination and clarifying that the safety of such vaccines in study participants receiving investigational agents is unknown.
Section 8.1.3, Post Study Treatment Study Follow-up; Section 9.1.2 Patient-reported Outcomes	Specified that participants will continue to be followed for safety and removed text about Survival Follow-up.	These changes were made to clarify the removal of Survival Follow-up for the study.
Section 9, Study Assessments and Procedures	• Updated text in Section 9.1 to clarify discontinuation of efficacy assessments. • Added text in Section 9.5 about discontinuing on-treatment and post-treatment pharmacokinetics sample collection. • Added text in Section 9.6 about discontinuing on-treatment and post-treatment pharmacodynamic assessment collection. • Added text in Section 9.8 about discontinuing on-treatment and post-treatment biomarker assessment collection.	These changes were made to clarify the removal of collection of biological samples (non-safety) for the study. Samples will not be collected going forward in this protocol, but samples collected prior to implementation of Protocol Amendment 07, may be retained for additional research.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2, Study Governance Considerations	• Added text about remote monitoring. • Added text on the dissemination of clinical study data.	• These changes were made to clarify conditions where remote monitoring can be considered. • These changes were made to clarify disclosure of study data in compliance with national and international standards.
All	Minor formatting and editorial changes.	Minor edits that do not change the content of the protocol were made to improve readability and consistency; therefore, they have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Master Protocol

Protocol Title: A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants with Advanced Renal Cell Carcinoma (FRACTION-RCC)

Study Phase: 2

Rationale:

The FRACTION Program will consist of several FRACTION studies, each in a specific tumor type and with a well-defined participant population. Each FRACTION study will have a Master Protocol, which will apply to all study treatment combinations selected for evaluation under that tumor-specific FRACTION study and any control treatments. For the FRACTION Program, it is intended that combination agents will be immuno-oncology (IO) agents within the Bristol-Myers Squibb Company (BMS) pipeline or IO agents already approved; however, they may also include small molecule agents or other modalities for which there is scientific rationale for combining with an IO agent in a given disease. All novel FRACTION combinations will be selected based on sound scientific rationale, supported whenever possible and appropriate by in vivo model systems, to demonstrate anti-cancer activity and preliminary assessments of clinical tolerability.

Specific study treatment combinations and/or control treatments will be introduced in FRACTION Sub-Protocols for each FRACTION study; these Sub-Protocols will be appended to the Master Protocol for that study and will include information appropriate to the study treatment combinations and/or control treatments being added to the study, including the preclinical rationale, preclinical toxicology and clinical safety data, as well as pharmacokinetic and pharmacodynamic information, as available. Thus, for the FRACTION Program, study treatment combinations that have high potential to produce transformational activity compared to the control, based on both preclinical and early clinical trials data, will be selected. Other studies in the FRACTION Program, Study CA018001, "Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Subjects with Advanced Non-small Cell Lung Cancer (FRACTION-Lung)," and CA018003, "A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants with Advanced Gastric Cancer (FRACTION-Gastric Cancer)" have been closed.

Study Population:

The study population consists of participants with advanced (not amenable to curative surgery or radiation treatment) or metastatic (American Joint Committee on Cancer Stage IV) RCC and have histological confirmation of RCC with a clear-cell component. In Track 1, participants must not have received any anti-programmed death 1 (PD-1), anti-programmed cell death ligand 1 (PD-L1), or anti-cytotoxic T lymphocyte antigen 4 (CTLA)-4 treatment prior to this study (participants previously treated with agents other than anti-PD-1, anti-PD-L1, or anti-CTLA-4 are eligible for Track 1). Track 1 participants with favorable risk profile by IMDC Score must have been treated with sunitinib prior to randomization into Track 1 nivolumab plus ipilimumab.

Track 2 participants must have had progressive or recurrent disease during or after anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment (participants treated with any study treatment targeting PD-1, PD-L1, or CTLA-4 will be considered anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experienced, respectively). All participants must allow a tumor biopsy at the following time points: 1) baseline (prior to study treatment); 2) on-study (Day 28 On-treatment); and 3) end of treatment (EOT), defined as at the time of progression or at the time of a clinically significant event (eg, at EOT for participants with partial response (PR) or stable disease or at EOT for participants who discontinue treatment due to an AE) provided that the biopsy is an acceptable clinical risk as judged by the investigator for each study treatment regimen.

Participants must meet the following criteria:

- Must be 18 years of age or older with inoperable, advanced or metastatic RCC
- RCC must be histologically confirmed with a clear cell component.
- Life expectancy of at least 3 months
- Must be evaluated for risk of the disease as defined by International Metastatic RCC Database Consortium (IMDC) score (Appendix 8).
- If they have received prior palliative radiotherapy to a non-CNS, treatment must be completed 2 weeks prior to first dose.
- Must have at least one measurable lesion (if the only measurable lesion has been irradiated, the lesion must have demonstrated clear progression and be measurable).
- Must agree to 3 biopsies during the study as described in protocol.
- Toxicities from previous anti-tumoral therapy should be resolved to Grade 1. Exceptions such as alopecia and fatigue, as well as long term toxicities which result in sequelae, such as neuropathies, are allowed.
- Must have adequate organ function as reflected by WBC, neutrophils, creatinine, bilirubin, hemoglobin, ALT, and AST.
- Must not have prior active malignancy in the last 3 years, except locally curable cancer that has been cured.
- Must not have received any anti-cancer therapy during the 4 weeks prior to the first dose of study treatment.
- Must not have suspected, known, progressive or untreated CNS metastasis, or CNS as only site of disease, unless it has been adequately treated and neurologically returned to baseline.
- Must not have an autoimmune disease or adrenal insufficiency and must not have received corticosteroids or immunosuppressive therapy within 14 days of study treatment administration.
- Must not have experienced prior life-threatening toxicities to IO therapy, have significant cardiac disease as described in the protocol, or interstitial lung disease.
- Women of child bearing potential and males who are sexually active must adhere to the guidelines set forth in the protocol (Appendix 4).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy (ORR, DOR, and PFSR at 24 weeks) of each FRACTION-RCC study treatment combination (relative to nivolumab in combination with ipilimumab, when applicable) in participants with advanced RCC	• ORR defined as the proportion of all treated participants with a BOR of CR or PR as assessed per RECIST v1.1 by investigator, median DOR, and PFSR at 24 weeks
Secondary	
• To investigate additional safety and tolerability of each FRACTION-RCC study treatment combination in participants with advanced RCC	• Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities

Abbreviations: AE = adverse event; CR = complete response; BOR = best overall response; DOR = duration of response; ORR = objective response rate; PFSR = progression-free response rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAE = serious adverse event.

Overall Design:

- This is a rolling, Phase 2, adaptive study that uses a control.
- This is an open-label study.
- Following screening, participants will be randomized to study treatment at Day 1, Week 1.
  - Participants who are naïve to anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment will be enrolled in Track 1, and they will be further randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-RCC study treatment combinations stratified by whether or not the participant has had prior TKI treatment.
  - Participants who have received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment will be enrolled in Track 2 and randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-RCC study treatment combinations. In addition, participants with progression of disease who were treated in Track 1 or 2 and continue to fulfill all entry criteria may be enrolled in Track 2 and re-randomized to a new combination other than that previously received, if applicable. Re-randomization is not applicable per Protocol Amendment 07.

Number of Participants:

In Track 1, up to 63 anti-PD-1/PD-L1 or anti-CTLA-4 treatment-naive participants will be treated per study treatment combination. In Track 2, up to 41 participants will be treated per study treatment combination.

Sample sizes are guided by Simon 2-stage (optimal) designs. Because of the different participant populations (anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment-naïve versus anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment-experienced) and existing care options under each Track,

different criteria are applied to determine the number of participants for each stage and the strength of the efficacy signal that would recommend proceeding to the next stage.

For sample size calculation and for simplicity of description, recommendations for stopping or progressing to the next stage are based on the number of objective responses observed. However, since best overall response does not necessarily capture the full extent of clinical benefit and since response can be delayed or of short duration, the BMS Medical Monitor (or designee) will also review other aspects of clinical benefit that may better predict overall survival benefit, such as duration of response and progression-free survival rate, as well as the relative performance of different study treatment combination arms, before making a final determination.

Enrollment may continue after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response or for additional considerations that may be needed in Stage 2 such as PK/PD analyses. In such cases, the total number of participants enrolled will not exceed the specified total number of participants treated in that arm according to Simon 2 stage.

Although the sample size calculations are based on efficacy considerations, safety will also be continuously assessed and will be taken into account in the decision to continue or terminate a study treatment arm. In Track 2, 41 participants per study treatment arm in Stages 1 and 2 combined will result in 88% probability of detecting an adverse event (AE) that has a true rate of 5%. More participants per study treatment arm in Stages 1 and 2 combined will result in a higher probability of detecting an AE that has a true rate of 5%.

With regard to sample size, participants who are re-randomized to a different study treatment in Track 2 will be counted once for each randomization; participants who are retreated within the same study treatment arm will only be counted once.

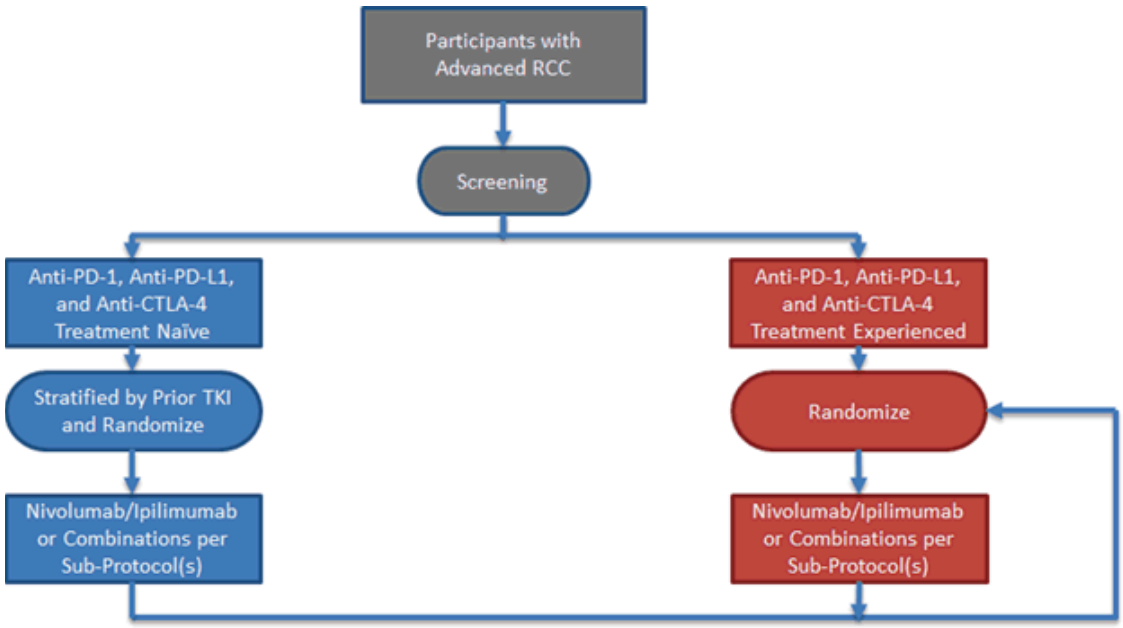
Enrollment will be continued during initial efficacy evaluation (ie, with the indicated number of participants at Stage 1) to allow additional participants to enroll to account for unexpected trial impact, such as response non-evaluable participants due to early drop-out, design parameter change (eg, historical rate update), etc.

Treatment Arms and Duration:

Study treatment:

A table describing the study treatments and dosage information is provided in each FRACTION-RCC Sub-Protocol.

Figure 1-1: Study Design Schematic



Note: Participants treated with any study treatment targeting PD-1, PD-L1, or CTLA-4 will be considered anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experienced, respectively.

Re-randomization is no longer applicable per Protocol Amendment 07.

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

- The total study duration is approximately 7 years and 18 weeks (up to 28-day Screening Phase, 2-year Treatment Phase, 100-day Safety Follow-up Phase, up to 2-year Response Follow-up Phase in parallel with up to 5-year Survival Follow-up Phase), not considering re-randomization and retreatment. Two-year Response Follow-up to 5-year Survival Follow-up Phase is not applicable per Protocol Amendment 07.
- Participants can receive study treatment for a total duration of approximately 2 years (approximately 48 weeks of total treatment) with their Track 1 or 2 randomized study treatment combination.
- Specific dosing and treatment regimens for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are outlined in each FRACTION-RCC Sub-Protocol.
- Guidelines for dose reductions and delays due to toxicity and for resuming study treatment for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are provided in each FRACTION-RCC Sub-Protocol.
- Participants will generally be allowed to continue study treatment until the first occurrence of one of the following: 1) completion of approximately 2 years of study treatment, 2) progressive disease (subject to treatment beyond progression, as detailed in Section 7.4.2 of the FRACTION-RCC Master Protocol), 3) clinical deterioration suggesting that no further benefit from study treatment is likely, 4) intolerable toxicity, 5) meeting of criteria for discontinuation

of study treatment, as outlined in Section 8.1 of the FRACTION-RCC Master Protocol. Additional study treatment-specific discontinuation criteria are provided in each FRACTION-RCC Sub-Protocol.

- Two independent committees may be utilized: a Safety Monitoring Board and an Independent Review Committee.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 (Screening Procedural Outline), Table 2-2 (Baseline for Re-randomization Procedural Outline) - Not applicable per Protocol Amendment 07, and Table 2-3 (Follow-up Procedural Outline). The On-treatment Procedural Outline(s) and exceptions for study treatment combination arms are included in each Fast Real-time Assessment of Combination Therapy in Immuno-Oncology for renal cell carcinoma (FRACTION-RCC) Sub-Protocol.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest priority to lowest:

- Safety (clinical laboratory examinations)
- Safety (electrocardiogram [ECG])
- Biomarker sampling
- Pharmacokinetic (PK) and anti-drug antibody (ADA) sampling

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Obtain patient identification number via IRT after signing of the written informed consent.
Utilize IRT	X	Obtain patient identification number. After completing all screening procedures, utilize IRT to either screen fail or obtain randomization information, as applicable. Randomization can occur up to 5 - 7 days prior to first dose. In limited circumstances, if patients cannot be treated within 5 - 7 days of randomization due to a study-related test, the duration can be extended after discussion with the BMS Medical Monitor (or designee).
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	Includes prior conditions and any toxicities or allergies related to previous treatments.
Collect Data on Prior Anti-PD-1, Anti-PD-L1, or Anti-CTLA-4 Treatment Exposure	X	Prior to screening for the protocol, investigative sites are required to determine the participant's exposure to anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment. Those data will be collected as part of the Screening Phase. Toxicities from prior immunotherapies with details on timing, treatment, and resolution, if applicable, should be captured.
Prior Therapy	X	Radiotherapy/surgery/systemic therapy administered for the treatment of RCC
Safety Assessments		
Physical Examination	X	If the screening physical examination is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation.
Oxygen Saturation	X	Record at rest and after mild to moderate exertion via pulse oximetry to establish baseline. If participant has oxygen saturation ≤ 90%, consult the BMS Medical Monitor (or designee) prior to enrollment.
Physical Measurements	X	Includes height and weight.
Vital Signs	X	Obtain vital signs at the screening visit and within 72 hours prior to first dose of assigned treatment. Includes body temperature, respiratory rate, seated blood pressure, and heart rate.
Risk information	X	Defined by International Metastatic RCC Database Consortium (IMDC) score (Appendix 8). This score will be retrospectively collected for participants randomized prior to protocol revision, if possible.

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Karnofsky Performance Status	X	
12-lead ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Record QTcF. If ECG abnormality is noted, a repeat ECG must be performed.
Chest x-ray	X (see note)	Optional. Baseline chest x-ray (for future comparison) may be performed if considered to be clinically relevant per standard of care
Concomitant Medication Collection	X	Includes medications taken within 14 days prior to assigned study treatment.
Assessment of Baseline Signs and Symptoms	X	Assess within 14 days prior to first dose of study treatment.
Laboratory Tests		Includes blood and urine samples.
Hematology	X	Includes CBC with differential including platelets.
Serum Chemistry[b]	X	See Section 9.4.1.
Thyroid Function Panel[b]	X	If TSH is abnormal, then obtain free T3 and free T4.
Methemoglobin	X	Methemoglobin should be tested prior to the start of study treatments
Glucose-6-phosphate Dehydrogenase Deficiency Testing	X	Glucose-6-phosphate dehydrogenase should be tested prior to the start of study treatment.
Serology	X	Perform testing for Hepatitis A IgM and IgG antibodies, HBsAg, hepatitis C antibody (if hepatitis C antibody is positive, reflex to hepatitis C RNA), or hepatitis C RNA. (Note: Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements.)
Pregnancy Serum or Urine Test	X	For WOCBP only. Serum or urine, within 24 hours prior to first dose of assigned study treatment. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Follicle Stimulating Hormone	X	For women only. Refer to Appendix 4.

Table 2-1: Screening Procedural Outline

Procedure	Screening Visit[a]	Notes
Mandatory Pretreatment Tumor Biopsy	X	Biopsy must be performed during the Screening Phase in all participants prior to first dose of assigned study treatment. Sample(s) may be retained for additional research. Sufficient tumor tissue must be obtained before start of study treatment from a primary or metastatic site. Tumor tissue samples must be shipped from site to central laboratory prior to randomization. (Note: Fine needle aspiration and bone metastases samples are not acceptable for submission.)
Archival Tumor Tissue Block	X	An archival, formalin-fixed, paraffin-embedded tumor tissue block (preferred) or a minimum of 20 slides of samples from a primary or metastatic site should be provided by all participants, if available.
Efficacy Assessment		
Baseline Tumor Assessment	X	Assessed by RECIST v1.1 criteria (see Appendix 5) Disease assessment with contrast-enhanced CT/MRI scans acquired on dedicated CT/MRI equipment is preferred for this study. CT or MRI of the chest, abdomen, pelvis, and all known sites of disease should be performed within 28 days prior to the first dose of study treatment. Assessment must include other anatomic regions as indicated based on the participant's tumor type and/or disease history. Participants with a history of brain metastasis should have an MRI (preferred) or CT of the brain. Participants with a history of bone metastasis should have a bone scan.
AE Reporting		
SAEs	X	All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. All SAEs and AEs will be assessed using NCI CTCAE Version 4.03.

[a] Within 28 days of first dose of assigned study treatment unless specified in notes section.

[b] If a participant is screened and begins study treatment within 3 days, the laboratory assessments for the Screening Phase can be used for Day 1 of the On-treatment Procedural Outline in each FRACTION-RCC Sub-Protocol as well.

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb Company; CBC = complete blood count; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTLA-4 = cytotoxic T lymphocyte antigen; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IRT = Interactive Response Technology; MRI =magnetic resonance imaging; NCI = National Cancer Institute;

PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; QTcF = QT interval corrected with Fridericia's formula; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of child-bearing potential.

Table 2-2: Baseline for Re-randomization Procedural Outline (Not applicable per Protocol Amendment 07)

Procedure	Days -1 to -28[a]	Notes
Eligibility Assessments	X	Participants must continue to meet eligibility criteria; otherwise, discuss with the BMS Medical Monitor (or designee). All inclusion/exclusion criteria should be assessed at the re-treatment/re-randomization baseline visit and confirmed prior to first dose.
Informed Consent	X	Participants must sign informed consent for re-randomization.
Participant Registration for Re-randomization	X	Ensure participant continues to meet eligibility for study treatment.
Safety Assessments		
Physical Examination	X	If the re-randomization baseline physical examination is performed within 24 hours prior to dosing on Day 1, then a single examination may count as both the re-randomization baseline and predose evaluation.
Physical Measurements	X	Includes weight.
Vital Signs	X	Includes body temperature, seated blood pressure, and heart rate.
Karnofsky Performance Status	X	
12-lead ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Record QTcF. If ECG abnormality is noted, a repeat ECG must be performed.
Concomitant Medication Collection	X	Includes medications taken within 14 days prior to study treatment
Oxygen Saturation	X	Record at rest and after mild to moderate exertion via pulse oximetry to establish baseline. If participant has oxygen saturation ≤ 90%, consult the BMS Medical Monitor (or designee) prior to entering re-randomization.
Assessment of Baseline Signs and Symptoms	X	If re-baseline or re-randomization occurs > 100 days after the last dose, signs and symptoms that occur up to 14 days prior to the next dose of study treatment should be recorded.
Risk information	X	Defined by International Metastatic RCC Database Consortium (IMDC) score (Appendix 8). This score will be retrospectively collected for participants randomized prior to protocol revision, if possible.

Table 2-2: Baseline for Re-randomization Procedural Outline (Not applicable per Protocol Amendment 07)

Procedure	Days -1 to -28[a]	Notes
Laboratory Tests		Includes blood and urine samples.
Hematology	X	Includes CBC with differential including platelets.
Serum Chemistry[b]	X	See Section 9.4.1.
Thyroid Function Panel[b]	X	If TSH is abnormal, then obtain free T3 and free T4.
Methemoglobin	X	Methemoglobin should be tested prior to the start of study treatments
Glucose-6-phosphate Dehydrogenase Deficiency Testing	X	Glucose-6-phosphate dehydrogenase should be tested prior to the start of study treatment.
Serology	X	Serology must be collected if > 6 months has passed since the previous assessment. Perform testing for Hepatitis A IgM and IgG antibodies, HBsAg, hepatitis C antibody (if hepatitis C antibody is positive, reflex to hepatitis C-RNA), or hepatitis C-RNA. (Note: Testing for HIV-1 and HIV-2 must be performed at site where mandated by local requirements.)
Pregnancy Serum or Urine Test	X	For WOCBP only. Serum or urine, within 24 hours prior to first dose of assigned study treatment. An extension up to 72 hours prior to start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.
Follicle Stimulating Hormone	X	For women only. Refer to Appendix 4.
Mandatory Pretreatment Tumor Biopsy	X	A mandatory pretreatment fresh tumor biopsy must be performed if a progression biopsy from the current study is not available. Sufficient tumor tissue must be obtained before start of study treatment from a primary or metastatic site. Tumor tissue samples must be shipped from site to central laboratory prior to re-randomization. (Note: Fine needle aspiration and bone metastases samples are not acceptable for submission.)

Table 2-2: Baseline for Re-randomization Procedural Outline (Not applicable per Protocol Amendment 07)

Procedure	Days -1 to -28[a]	Notes
Efficacy Assessments		
Baseline Tumor Assessment	X	Assessed by RECIST v1.1 criteria (see Appendix 5) Disease assessment with contrast-enhanced CT/MRI scans acquired on dedicated CT/MRI equipment is preferred for this study. CT or MRI of the chest, abdomen, pelvis and all known sites of disease should be done within 28 days prior to first dose of study treatment. Assessment must include other anatomic regions as indicated based on the participant's tumor type and/or disease history. Participants with a history of brain metastasis should have an MRI (preferred) or CT of the brain. Participants with a history of bone metastasis should have a bone scan.
AE Reporting		
SAEs	X	All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. All SAEs and AEs will be assessed using NCI CTCAE Version 4.03.

[a] If a participant is screened and begins study treatment within 3 days, the laboratory assessments for the Screening Phase can be used for Day 1 of the On-treatment Procedural Outline in each FRACTION-RCC Sub-Protocol as well.

[b] Within 28 days of first dose of assigned study treatment unless otherwise specified in notes section.

Abbreviations: AE = adverse event; BMS = Bristol Myers Squibb Company; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FRACTION = Fast Real-time Assessment of Combination Therapy in Immuno-Oncology; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NCI = National Cancer Institute; PK = pharmacokinetic; QTcF = QT interval corrected with Fridericia's formula; RCC = Renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of child-bearing potential.

Note: On-treatment Procedural Outlines are in the relevant FRACTION-RCC Sub-Protocol.

Table 2-3: Follow-up Procedural Outline

Procedure	Safety Follow-up			Response/Survival Follow-up	Notes
	FU 1 30 Days[a] (± 7 Days)	**FU 2 60 Days (± 7 Days)**	**FU 3 100 Days (± 7 Days)**	**Begins after Completion of Safety Follow-up Every 12 Weeks (± 2 Weeks) until 2 Years after Last Dose[b]**	
Safety Assessments					
Physical Examination	X	X	X		
Oxygen Saturation	X	As clinically indicated			Record at rest and after mild to moderate exertion via pulse oximetry
Vital Signs and Weight	X	X	X		Includes body temperature, seated blood pressure, and heart rate.
Karnofsky Performance Status	X	X	X		
Review of Concomitant Medications	X	X	X		
Laboratory Tests					
Hematology and Serum Chemistry	X		X		
PK Samples[c]	X				Details are provided in each FRACTION-RCC Sub-Protocol
Anti-drug Antibody Samples[c]	X				Details are provided in each FRACTION-RCC Sub-Protocol
AE Reporting					
Monitor for Nonserious AEs	X	X	X		Nonserious AEs must be collected from first dose until 100 days following the last dose of study treatment. All SAEs and AEs will be assessed using NCI CTCAE Version 4.03.

Table 2-3: Follow-up Procedural Outline

Procedure	Safety Follow-up			Response/Survival Follow-up	Notes
	FU 1 30 Days[a] (± 7 Days)	**FU 2 60 Days (± 7 Days)**	**FU 3 100 Days (± 7 Days)**	**Begins after Completion of Safety Follow-up Every 12 Weeks (± 2 Weeks) until 2 Years after Last Dose[b]**	
Monitor for SAEs	X	X	X		All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. All SAEs and AEs will be assessed using NCI CTCAE Version 4.03.
Efficacy Assessments					
Tumor Response Assessment[c]	X		X		Assessed by RECIST v1.1 criteria (see Appendix 5). Participants with a history of brain metastasis should have an MRI (preferred) or CT of the brain if clinically indicated. Participants with a history of bone metastasis should have a bone scan if clinically indicated. All participants should receive scans at FU1, or 30 days (+ 7 days), except for participants with PD who started subsequent therapy or have already been treated beyond progression. Scans at FU3, or 100 days (+ 7 days), and every 12 weeks (+ 14 days) will only be collected for participants with CR, PR, or SD at treatment discontinuation.

Table 2-3: Follow-up Procedural Outline

Procedure	Safety Follow-up			Response/Survival Follow-up	Notes
	FU 1 30 Days[a] (± 7 Days)	**FU 2 60 Days (± 7 Days)**	**FU 3 100 Days (± 7 Days)**	**Begins after Completion of Safety Follow-up Every 12 Weeks (± 2 Weeks) until 2 Years after Last Dose[b]**	
Patient-reported Outcomes Assessment[c]	X	X	X		EQ-5D-3L and FKSI-DRS Can be collected over the phone at regularly scheduled time if needed.
Collection of Survival Status and Subsequent Treatment Information[c]	X	X	X		Safety follow-up visits must occur in the office. Response (and survival) follow-up visits may be performed by telephone contact or clinic visit.

[a] FU visits at Days 30, 60, and 100 (± 7 days) should occur after the last dose of study treatment or coinciding with the date of discontinuation ± 7 days, if the date of discontinuation is greater than 30 days after the last dose, to monitor for AEs.

[b] Not applicable per Protocol Amendment 07: Additional survival follow-up will be collected every 6 months for 3 additional years (2 years of response follow-up + 3 years of survival follow-up = total of 5 years of follow-up). BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up. Withdrawal of consent must be clearly documented. See Section 5.1.3.3 for details.

[c] Per Protocol Amendment 07: Assessments necessary for monitoring safety (eg, safety laboratory assesments, oxygen saturation, vital signs, physical examinations, review of concomitant medications, AE/ SAE reporting, etc) will continue per sub-protocol until the FU 3 visit. Tumor scans, survival status follow-ups, and collection of subsequent treatment information will end once the participant has disease progression or treatment discontinuation for any reason, whichever occurs first. Collection of samples for PK and ADA, as well as collection of data for patient-reported outcomes, should be discontinued.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMS = Bristol Myers Squibb Company; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D-3L = European Quality of Life self-report questionnaire 3-level version; FKSI-DRS = Functional Assessment of Cancer Therapy-Kidney Symptom Index-disease-related symptoms; FRACTION = Fast Real-time Assessment of Combination Therapy in Immuno-Oncology; FU = follow-up; MRI = magnetic resonance imaging; NCI = National Cancer Institute; PK = pharmacokinetic; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

3 INTRODUCTION

Traditional or conventional treatment options for patients with advanced cancer include surgery, radiation, chemotherapy, and hormonal therapy. Despite advances in these therapies, the majority of patients with metastatic disease die from progressive disease. Immunotherapeutic approaches have demonstrated clinical efficacy and have been approved in multiple countries worldwide and in several solid tumor malignancies, including melanoma, renal cell, lung, and hormone-refractory prostate cancers.[1,2] Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T-cell checkpoint regulators such as cytotoxic T-lymphocyte antigen 4 (CTLA-4; see Appendix 1) and programmed death-1 (PD-1, cluster of differentiation [CD] 279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades that downregulate T-cell activation and proliferation. One proposed model by which therapeutic T-cell checkpoint inhibitors derive anti-tumor activity is through breaking of immune tolerance to tumor cell antigens by T-cell activation and proliferation.

Following on the success of anti-CTLA-4 and anti-PD-1 pathway-targeted agents in several cancers, the field of tumor immunotherapy is rapidly expanding. [redacted] Members of the tumor necrosis factor receptor super family (TNFRsf) include several co-stimulatory proteins with key roles in B- and T-cell development, survival, immune activation, and anti-tumor immune responses.[4] Preclinical data have provided the basis for clinical studies of agonist antibodies to such TNFRsf co-stimulatory receptors such as 4-1BB,[5,6] OX40,[7,8] glucocorticoid-induced tumor necrosis factor receptor-related (GITR) gene,[9,10] and CD27[11,12] along with a growing list of immuno-oncology (IO) targets that modulate other immunomodulatory mechanisms as potential therapies for patients with cancer. Overall, enhancement of the magnitude and potency of tumor antigen-specific adaptive cellular responses by CD8 and CD4 T-cells is now considered a major goal in cancer immunotherapy.

With emerging clinical data showing significant activity of single-agent immunotherapies, it is possible, and indeed likely, that combination therapies could potentially lead to a greater depth of response and an increase in overall survival (OS) as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in participants with advanced melanoma and renal cell carcinoma (RCC).[13,14,15,16] This raises the possibility that combining agents with a broader range of relevant targets, eg, checkpoint blocking antibodies with agonist antibodies to T-cell co-stimulatory molecules and immunomodulatory agents, is likely to lead to durable, long-term responses and possibly even cures in this high unmet medical need population of patients with metastatic or refractory tumors. Preclinical data from evaluation of combinations in mouse tumor models indicate that treatment with a combination of IO agents may lead to enhanced anti-tumor activity above that from each agent alone.[17] Thus, a combination of IO agents has the potential to provide clinical benefit to such patients with high unmet medical needs.

3.1 Study Rationale

3.1.1 FRACTION Program

3.1.1.1 Rationale for the FRACTION Program

Bristol-Myers Squibb Company (BMS) has an extensive portfolio of novel agents that spans a variety of targets. Within the immune system, these include T-cell checkpoint inhibitors, co-stimulatory molecules acting on T-cells, regulatory T-cell and natural killer (NK) cell-targeted agents, treatments that alter the tumor microenvironment to favor a tumor inhibitory milieu, and treatments that target myeloid-derived suppressor cells or tumor-associated macrophages. In addition to agents that target the immune system, BMS has a portfolio of agents that directly target tumor cells. These include antibody drug conjugates and both biologic and small molecule inhibitors of key signaling pathways. In fact, the number of compounds to be evaluated has grown so large that it is no longer possible or efficient to test all possible combinations in a standard clinical Phase 1 or Phase 2 setting.

To determine which combinations show the most clinical promise and thus should be prioritized for registrational studies, BMS has initiated the FRACTION Program (globally listed under the descriptor, BMS-986217). The FRACTION Program will employ repeat core biopsies and serial assessments with different treatment options. These approaches are supported by the National Cancer Institute (NCI) Biomarker integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program,[18] the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis (I-SPY 1/2 TRIAL),[19] the Lung-MAP: S1400 Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IIIB-IV Squamous Cell Lung Cancer (NCT02154490),[20] the NCI Molecular Analyses for Therapy Choice (NCI-MATCH, NCT02465060), and the American Society of Clinical Oncology's Targeted Agent and Profiling Utilization Registry (TAPUR).[21] These studies use innovative trial designs to quickly assess new agents in participants with the goal of reducing the time and number of participants required to bring these therapies to those who will benefit from them.

The FRACTION Program will consist of several FRACTION studies, each in a specific tumor type and with a well-defined participant population. Each FRACTION study will have a Master Protocol, which will apply to all study treatment combinations selected for evaluation under that tumor-specific FRACTION study and any control treatments. For the FRACTION Program, it is intended that combination agents will be IO agents within the BMS pipeline or IO agents already approved; however, they may also include small molecule agents or other modalities for which there is scientific rationale for combining with an IO agent in a given disease. All novel FRACTION combinations will be selected based on sound scientific rationale, supported whenever possible and appropriate by in vivo model systems, to demonstrate anti-cancer activity and preliminary assessments of clinical tolerability.

Specific study treatment combinations and/or control treatments will be introduced in FRACTION Sub-Protocols for each FRACTION study; these Sub-Protocols will be appended to the Master Protocol for that study and will include information appropriate to the study treatment combinations and/or control treatments being added to the study, including the preclinical

rationale, preclinical toxicology and clinical safety data, as well as PK and pharmacodynamic information, as available. The minimum preclinical safety information provided in each Sub-Protocol will include the definitive studies that were used to support the health authorities, review for each individual agent, along with any additional preclinical safety studies that were conducted subsequent to the original applications. In addition, the toxicology rationale to support each combination will be discussed. For each agent, the established monotherapy and relevant combination clinical safety package from studies done outside of FRACTION will be included. Participants within the FRACTION Program will not be the first to be exposed to any treatment.

Thus, for the FRACTION Program, study treatment combinations that have high potential to produce transformational activity compared to the control, based on both preclinical and early clinical trials data, will be selected. Other studies in the FRACTION Program, Study CA018001, "Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Subjects with Advanced Non-small Cell Lung Cancer (FRACTION-Lung)," and CA018003, "A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants with Advanced Gastric Cancer (FRACTION-Gastric Cancer)," have been closed.

3.1.1.2 Specific Attributes of the FRACTION Program Design

The specific attributes of the FRACTION Program include the following:

- An innovative study design providing participants with advanced cancer the possibility of expeditious access to innovative therapies, including combinations with approved treatments like nivolumab. In addition, it will provide an ongoing treatment option for participants across the spectrum of their disease as they progress through the FRACTION Program, as participants can enter into different treatment "Tracks" based upon their treatment exposure and response.
- A streamlined decision-making process allowing for more rapid and efficient selection of promising treatment options in BMS's evolving portfolio of oncology assets. This extensive pipeline of novel targets and/or agents could result in an excess of 100 individual monotherapy and doublet combinations in need of study. The challenges to study all possible combinations in a traditional clinical program are daunting, especially since animal models and/or biomarker data still cannot effectively predict participant responses. This means that clinical exploration in participants is required if it is to be truly informative and ultimately lead to participant benefit. Thus, FRACTION is designed as a way to explore and compare multiple IO combinations against each other and against a control treatment.
- A Master Protocol, in conjunction with appended FRACTION Sub-Protocols, allowing for operational efficiencies for the rapid and efficient opening of new study treatment combination arms and closing of other study treatment combination arms that have demonstrated unacceptable toxicity or futility.
- A continuous throughput design allowing data to be available sooner to support either closure of study treatment combination arms (initial signal-seeking arms) or adaptively increasing sample size for further investigation with additional eligibility criteria and statistical considerations in a new sub-protocol if promising efficacy is seen with a treatment combination. This will drive and improve selection and acceleration of optimal combinations to help patients with cancer in dire need of new effective treatment options.

3.1.1.3 Rationale for Biomarker Assessments

There will be a core group of biomarker assessments (from both the peripheral blood and the tumor) that will apply to all novel FRACTION Program study combinations so that comparisons of such data can be made across different study treatments. The goals of the biomarker assessments proposed in the FRACTION Program are to 1) identify predictive biomarkers for both safety and efficacy of a given combination, 2) define the mechanism of action for a particular combination (pharmacodynamic assessment), and 3) determine the mechanisms of resistance to a particular combination. In addition, there will be biomarker assessments that are applied specifically for a given combination as dictated by the biology of the combination. The biomarker assessments can be grouped as follows:

1) *Blood-based biomarkers:* Peripheral blood will be obtained prior to and at defined time points during treatment (additional details are outlined in Section 9.8) including, but not limited to, the following:
   a) Multiparameter flow cytometry to assess the phenotype and functional/activation status of the immune-effector cells (including, but not limited to, discrete T-cell, myeloid, and NK cell populations) in the peripheral blood and how they are altered by study treatment.
   b) Proteomic assessment of various immunologically relevant cytokines, chemokines, soluble receptors/proteins, and potentially tumor-specific auto-antibodies, which may provide important pharmacodynamic parameters (eg, elicitation of interferon gamma (IFNγ)-dependent chemokines representing T-cell activation) as well as exploratory information.
   c) T-cell receptor sequencing will be performed to detect expansion of antigen-directed T-cells clones, which may provide evidence of adaptive immune responses against tumor and pharmacodynamics information potentially used for combination strategy.
   d) Specific biomarkers for a given asset/disease.
   e) Plasma ctDNA for Tumor Mutational Burden Assessment. High tumor mutational burden (TMB) is an indication for increased neo-antigen presentation in tumors, which leads to recruitment of immune cells to the tumor site and induction of anti-tumor immunity. Consequently, high TMB has been correlated with increased response to nivolumab and other therapeutics targeting the PD (L)1 axis in NSCLC. TMB can be inferred from ctDNA isolated from plasma samples. TMB results from the periphery will be compared with TMB results from whole exome sequencing of tumor tissue biopsies if sufficient slides are available. Quantitative and qualitative assessment of ctDNA can also provide insight into dominant tumor clones and their hierarchy, clonal evolution during treatment, and relevance for response and nonresponse. Plasma samples for ctDNA extraction will be collected at the indicated time points. and kept frozen at -80°C in storage. Additional use of these samples may include analysis of microsatellite instability or other clinically relevant biomarkers.
2) *Tumor tissue-based biomarkers:* Three mandatory biopsies are required at the following timepoints: 1) baseline (prior to study treatment); 2) on-study (Day 28 On-treatment); and 3) end of treatment (EOT), defined as at the time of progression or at the time of a clinically significant event (eg, at EOT for participants with partial response (PR) or stable disease (SD) or at EOT for participants who discontinue treatment due to an adverse event [AE]). (Details

regarding biopsy/processing and timing are outlined in Section 9.8.2.1). Archival tumor tissue blocks (preferred) or slides (a minimum of 20 slides) from a primary or metastatic site from all participants are to be provided, if available. The assessments to be performed on these fresh biopsies and archival tissue include, but are not limited to, the following:

a) Pathological assessment: to include immunohistochemical (IHC) and image analysis techniques and to understand the relationship between the type and geographic localization of immune effector cells and targets of interest in relation to the tumor and surrounding tissue.

b) Whole exome or whole genome sequencing: DNA may be extracted from biopsy specimens to monitor somatic mutations that may impact response and other efficacy measures. Whole exome, whole genome, or targeted sequencing methodologies may be employed. Tumor mutational load has been associated with response to immunomodulatory agents, including nivolumab.

c) Gene expression analysis: RNA-seq, and/or similar methodologies, will be used to assess gene expression patterns associated with each of the expansion tumor types and to identify changes in those gene expression patterns following treatments with. Ultimately, this approach may lead to the identification of unique baseline or on-treatment RNA expression signatures that could be useful for identifying patients who are likely (or unlikely) to respond to the combination therapy. Focus may be given to monitoring a battery of immunoregulatory genes associated with cancer cells or cancer-interacting lymphocytes. Examples within the latter group include genes associated with T-cells, NK cells, and/or IFN-γ signaling. Such genes have been implicated previously in tumor responses or rejection.

d) T-cell receptor sequencing of T-cells derived from the tumor (in conjunction with T-cell receptor sequencing of peripheral blood T-cells): to monitor the adaptive immune response against tumor and add to the pharmacodynamic information that would potentially be used in ranking promising combinations.

3.2 Background

3.2.1 FRACTION - RCC

Renal cell carcinoma (RCC) accounts for ~3% of all cancers in the US.[22] More than 60,000 patients will be diagnosed with RCC in a year, and approximately 13,000 patients will die from advanced disease.[23] Metastatic disease is found in 30% of participants at diagnosis. Close to 90% to 95% of metastatic disease is of the clear-cell histology.[24] With the increased use of imaging over the last several decades, the incidence of earlier stage and potentially more curable disease is rising.[23]

Multiple scoring systems are available to characterize prognosis in treatment-naïve RCC. Two of the most commonly used are the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system and the International Metastatic RCC Database Consortium (IMDC) prognostic scoring system.[25,26] Each of these systems categorizes patients as favorable, intermediate, or poor risk based on how many adverse prognostic factors are present (0: favorable risk, 1 to 2: intermediate risk, 3 or more: poor risk). The 6 parameters of importance for IMDC prognostic score classification are Karnofsky Performance Status (KPS), time from diagnosis to treatment, hemoglobin value, corrected calcium concentration, absolute neutrophil count, and platelet count.

The 5 parameters included in the MSKCC prognostic score are KPS, nephrectomy status, hemoglobin value, lactate dehydrogenase, and corrected calcium concentration. Time from diagnosis to treatment is often used in place of nephrectomy status. With each system, total number of adverse prognostic factors present has been shown to correlate with OS. Approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group (OS: ~9 months). In an analysis of 1,028 patients scored using the IMDC system, median OS for favorable-, intermediate-, and poor-risk patients is 43.2 months, 22.5 months, and 7.8 months, respectively.[27]

Until recently, the cytokines interleukin 2 (IL-2) and interferon alpha (IFNα) were the only active treatments for advanced or metastatic RCC. However, due to each of these agent's limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of advanced or metastatic RCC.[28,29,30,31] The recognition of the importance of hypoxia-inducible factor alpha (HIFα) signaling in the pathogenesis of clear-cell RCC has led to widespread study of 2 classes of targeted therapies, anti-angiogenic agents and mechanistic target of rapamycin (mTOR) inhibitors.[32] Targeting of angiogenesis is an appropriate rationale for treatment because constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF), which can subsequently lead to tumor proliferation and neovasculature formation. Targeting of the mTOR pathway is important because activation of the upstream PI3K/Akt/mTOR signaling pathway is one method by which constitutive HIFα activation or upregulation occurs. There are 7 agents for the treatment of RCC in the US and European Union (EU): 5 that target angiogenesis (ie, the VEGF-receptor tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib, and axitinib and the VEGF-binding monoclonal antibody bevacizumab plus interferon) and 2 that target the mTOR pathway (ie, everolimus and temsirolimus). Among these approved agents, none has demonstrated a statistically significant improvement in OS as a first-line therapy except for temsirolimus poor-risk patients. According to National Comprehensive Cancer Network guidelines, sunitinib, temsirolimus (poor-risk only), bevacizumab plus interferon, and pazopanib are Category 1 recommendations for first-line treatment of metastatic renal cell carcinoma (mRCC).[33] According to European Society for Medical Oncology guidelines, sunitinib, bevacizumab plus interferon, and pazopanib are all standard treatment options for favorable- and intermediate-risk patients, but sunitinib is the only one also considered an alternative to temsirolimus for the treatment of poor-risk patients.[34] Recently cabozantinib and levantinib have been approved in the US.

Immunotherapeutic approaches have demonstrated clinical efficacy in several advanced solid tumor cancers, including melanoma, non-small cell lung cancer (NSCLC), RCC, classical Hodgkin lymphoma, recurrent or metastatic sqamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, hepatocellular carcinoma and microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer.[35,36,37] Nivolumab (BMS-936558), a programmed cell death protein-1 (PD-1) antibody, and ipilimumab (BMS-734016), a cytotoxic T-cell lymphocyte antigen 4 (CTLA-4) antibody, are such immunotherapies that have been approved in the US, Europe, Japan, and other countries.[38,39,40,41]

Recently, nivolumab monotherapy was approved in the US, Canada, and Europe for the treatment of mRCC based on the results from Checkmate 025 (CA209025 A Randomized, Open-label, Phase III Study of *N*ivolumab versus Everolimus in Subjects with Advanced or Metastatic Clear-cell Renal Cell Carcinoma who have Received Prior Anti-Angiogenic Therapy, *NCT01668784*). In this study, 803 of the 821 randomized subjects were treated with either nivolumab (n = 406) or everolimus (n = 397). At a minimum follow-up period of 14 months, the median OS was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) in the nivolumab group and 19.6 months (95% CI, 17.6 to 23.1) in the everolimus group.[37] The OS benefit with nivolumab was observed across prespecified subgroups, including subgroups defined according to region, MSKCC prognostic score, and number of previous regimens of antiangiogenic therapy. The objective response rate (ORR) was higher with nivolumab than with everolimus (25% vs. 5%; odds ratio 5.98; 95% CI, 3.68 to 9.72; P < 0.001). PR were observed in 99 patients (24%) in the nivolumab group and in 20 patients (5%) in the everolimus group. Complete responses were observed in 4 patients (1%) in the nivolumab group and in 2 patients (< 1%) in the everolimus group. The median time to response was 3.5 months (range, 1.4 to 24.8) among the 103 patients with a response in the nivolumab group and 3.7 months (range, 1.5 to 11.2) among the 22 patients with a response in the everolimus group; the median duration of response was 12.0 months (range, 0 to 27.6) with nivolumab and 12.0 months (range, 0 to 22.2) with everolimus. The median progression-free survival (PFS)was 4.6 months (95% CI, 3.7 to 5.4) in the nivolumab group and 4.4 months (95% CI, 3.7 to 5.5) in the everolimus group (hazard ratio, 0.88; 95% CI, 0.75 to 1.03; P = 0.11). The median duration of treatment was 5.5 months (range, < 0.1 to 29.6) with nivolumab and 3.7 months (range, 0.2 to 25.7) with everolimus.

To date, nivolumab has been generally well tolerated, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[42]

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may further improve anti-tumor activity.[43] In vitro combinations of nivolumab plus ipilimumab increased IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4- and PD-1-expressing CD4/CD8 tumor-infiltrating T-effector cells, and dual blockade increased tumor infiltration of T-effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[22] In addition, combining immunotherapeutic agents with different mechanisms of action offers the possibility of further benefit as noted with the combination of PD-1 and CTLA-4 inhibitors in the treatment of patients with advanced melanoma.[13,15] In a Phase 1 study (CA209016 Phase 1 Open-Label, Parallel-group, Dose-escalation Study of Nivolumab in Combination With VEGFR-TKIs or IPI in Subjects with Metastatic RCC, NCT01472081) of nivolumab in combination with ipilimumab in mRCC, the combination of nivolumab and ipilimumab demonstrated acceptable safety and evidence of antitumor activity in mRCC.[44,45,46,47] Grades 3 and 4 events were manageable within established treatment guideline. The ORR suggests greater activity than reported previously with nivolumab

or ipilimumab monotherapy in RCC. Responses appear durable even after discontinuation of study treatment.[48]

Given the results of the Phase I study of nivolumab and ipilimumab, a Phase 3 study of nivolumab combined with ipilimumab was completed in patients with mRCC (CA209214 A Phase 3, Randomized, Open-label Study of Nivolumab Combined with Ipilimumab versus Sunitinib Monotherapy in Subjects with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma," NCT02231749). The co-primary objectives of this study were to compare ORR, progression-free survival (PFS) (based on Independent Radiology Review Committee assessment), and overall survival (OS) of nivolumab combined with ipilimumab to sunitinib monotherapy in intermediate and poor-risk participants with previously untreated mRCC. Combined immunotherapy with nivolumab plus ipilimumab resulted in a greater ORR (41.6% vs 26.5%, respectively [$P < 0.0001$]) and PFS (11.6 months vs 8.4 months, respectively, hazard ratio = 0.82 [$P = 0.03$]) compared to sunitinib in intermediate/poor-risk patients. Median OS was not reached in the nivolumab and ipilimumab arm and was 26.0 months in the sunitinib arm, a 37% reduction in the risk of death (HR, 0.63; 99.8% CI, 0.44-0.89; $P < 0.0001$). In those with PD-L1 expression > 1%, the median PFS was significantly longer with the immunotherapy combination than with sunitinib (22.9 vs 5.9 months; HR, 0.48; $P = 0.0003$). Findings support the use of combined nivolumab plus ipilimumab as a potential first-line treatment for patients with intermediate/poor-risk metastatic RCC, particularly those patients having tumor PD-L1 expression ≥ 1%.[49]

Taken together, these data support the use of nivolumab in combination with ipilimumab as a comparator and suggest that the use of nivolumab in combination with IO treatment has the potential to provide clinical benefit to such patients with advanced RCC (see FRACTION-RCC Sub-Protocols for details on further combinations).

This document will serve as the Master Protocol for the FRACTION-RCC Study (FRACTION-RCC; CA018005). As described above, novel study treatment combinations and/or additional controls will be appended as FRACTION-RCC Sub-Protocols. These FRACTION-RCC Sub-Protocols will evaluate the safety profile, tolerability, preliminary efficacy, PK, and pharmacodynamics of novel study treatment combinations in participants with advanced RCC. The initial control treatment in the FRACTION-RCC study will be nivolumab in combination with ipilimumab followed by nivolumab monotherapy.

3.3 Benefit/Risk Assessment

An overall risk/benefit assessment for each novel FRACTION-RCC study treatment combination will be provided in each FRACTION-RCC Sub-Protocol.

Non-live coronavirus disease 2019 (COVID-19) vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving investigational agents is unknown.

3.3.1 Safety Monitoring on Study Treatment

Frequent safety assessments will be carried out by the Sponsor/BMS Medical Monitor (or designee) and investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the study treatment combination arm is required at any time. In addition, AEs and serious adverse events (SAEs) will be reviewed regularly by the BMS Medical Monitor (or designee) and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow institutional guidelines and recommended management algorithms, as listed in the Investigator's Brochures (IBs) and prescribing information, as applicable, for each combination agent and control comparator, and provided as appendices to this protocol. Specific algorithms for the management of immune-related AEs are provided in Appendix 6 and are applicable to immune-related AEs for all FRACTION-RCC study treatment combinations.

4 OBJECTIVES AND ENDPOINTS

The overall FRACTION-RCC study-wide objectives are presented in the following sections. Any changes to these objectives for specific study treatments are specified in each FRACTION-RCC Sub-Protocol.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy (ORR, DOR, and PFSR at 24 weeks) of each FRACTION-RCC study treatment combination (relative to nivolumab in combination with ipilimumab, when applicable) in participants with advanced RCC	ORR defined as the proportion of all treated participants with a BOR of CR or PR as assessed per RECIST v1.1 by investigator, median DOR, and PFSR at 24 weeks
Secondary	
To investigate additional safety and tolerability of each FRACTION-RCC study treatment combination in participants with advanced RCC	Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and clinical laboratory test abnormalities
Tertiary/Exploratory	
• To assess the pharmacodynamic effects as a function of exposure, by evaluation of select biomarkers in the peripheral blood and tumor biopsy specimens • To explore potential associations between anti-tumor activity or safety and select biomarker measures in tumor biopsy specimens and peripheral blood prior to study treatment and following administration • To evaluate the PK of each IP component • To evaluate the immunogenicity of each IP, when applicable • To assess the OS in treated participants • To evaluate changes in disease-related symptoms, as measured by the FKSI-DRS, in treated participants	• Summary measures of change (or % change) from baseline or baseline level biomarker measurements in peripheral blood or tumor tissue • Correlation (or similar appropriate measure of association) of biomarker measure in peripheral blood or tumor tissue with parameters of interest • Summary measures of PK parameters from serum concentration. • Incidence of ADAs • OS rate at certain time points • Summary measures of EQ-5D-3L index scores, VAS scores, FKSI-DRS scores, and corresponding change from baselines for each score

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To evaluate general health, functional status, and utility for health using the EQ-5D-3L in treated participants	

Abbreviations: AE = adverse event; ADAs = anti-drug antibodies; CR = complete response; BOR = best overall response; DOR = duration of response; EQ-5D-3L = 3-level version of EQ-5D self-report questionnaire; FKSI-DRS = Functional Assessment of Cancer Therapy-Kidney Symptom Index-disease-related symptoms; FRACTION = Fast Real-time Assessment of Combination Therapy in Immuno-Oncology; IP = investigational product; ORR = overall response rate; OS = overall survival;; PFSR = progression-free survival rate; PK = pharmacokinetic; RCC = renal cell carcinoma; SAE = serious adverse event; VAS = visual analog scale.

AEs and laboratory values will be graded according to NCI CTCAE Version 4.03.

5 STUDY DESIGN

5.1 Overall Design

This is a rolling, Phase 2, adaptive study that will evaluate the preliminary efficacy, safety, tolerability, PK, and pharmacodynamics of novel FRACTION-RCC study treatment combinations in participants with advanced RCC. All novel treatment combinations will contain nivolumab. The details pertaining to the specific study treatment regimens are provided in each FRACTION-RCC Sub-Protocol.

Participants will be enrolled in 1 of 2 Tracks. Participants who are anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment naïve will be eligible for Track 1 and will be stratified by whether or not the participant has had prior TKI treatment. Participants who have had prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment will be assigned to Track 2, as outlined in Figure 5.1-1 and described in Section 5.1.1.

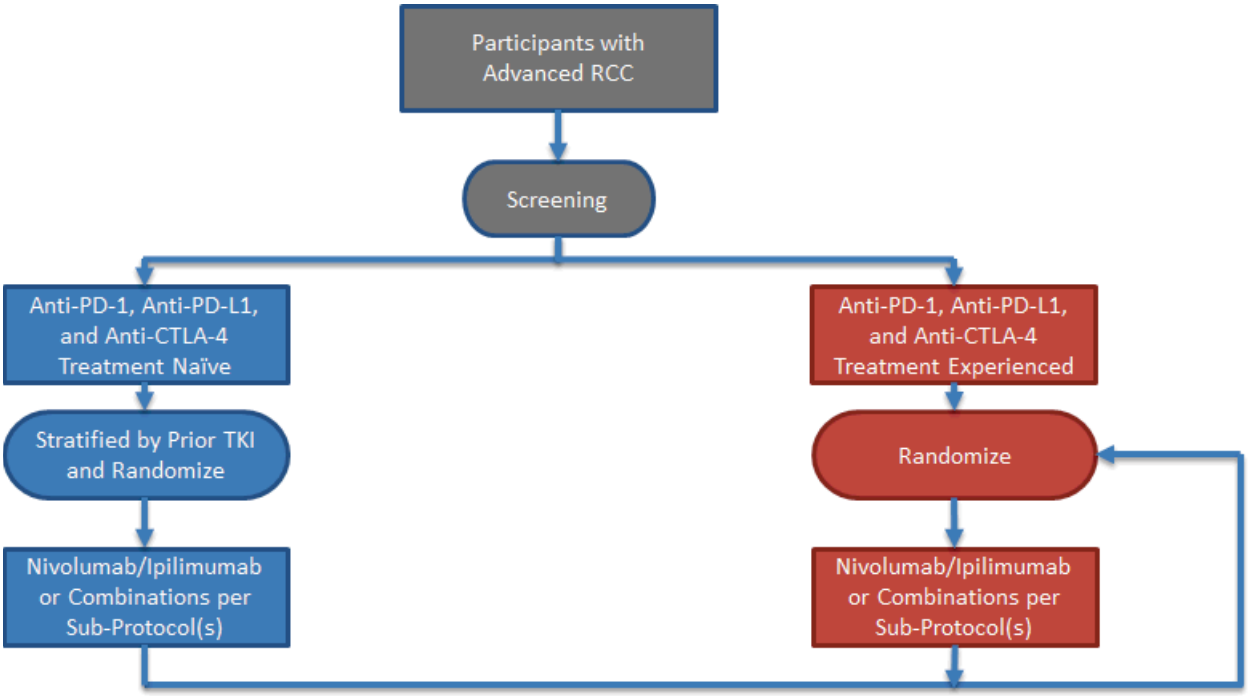
Participants on Tracks 1 and 2 will begin on the Treatment Phase (with a total duration of approximately 2 years). Tumor assessments will be conducted according to the timing described in each FRACTION-RCC Sub-Protocol.

Participants on Tracks 1 and 2 will be treated until completion of the Treatment Phase, progression, toxicity, or protocol-specified discontinuation (see Section 8.1).The decision to continue treatment beyond investigator-assessed progression is possible (for up to completion of that Treatment Phase) and should be discussed with the BMS Medical Monitor (or designee) and documented in the study records (see Section 7.4.2). In addition, a participant with progressive disease (PD) will have the option to enter into Track 2, assuming that he or she continues to fulfill all eligibility criteria at each new randomization point, including a life expectancy of ≥ 3 months (see Section 5.1.1). Re-randomization is no longer applicable per Protocol Amendment 07.

A Simon 2-stage (optimal) design will be used in both Tracks 1 and 2 to evaluate the possibility of terminating an arm early and/or moving promising combinations into the next phase of treatment development (see Section 10.1). Enrollment may continue after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response or for additional considerations that may be needed in Stage 2 such as PK/PD analyses. In such cases, the total number of participants enrolled will not exceed the specified total number of participants treated in that arm according to Simon 2 stage. The number of participants planned for enrollment may vary by Track and is described in Section 10.1. Participants who continue to fulfill eligibility criteria may move from Track 1 into Track 2 or re-enter Track 2, as described in Section 5.1.1.

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

Figure 5.1-1: Study Design Schematic



Note: Participants treated with any study treatment targeting PD-1, PD-L1, or CTLA-4 will be considered anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experienced, respectively.

Re-randomization is no longer applicable per Protocol Amendment 07.

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

Physical examinations, vital sign measurements, local 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout treatment on all Tracks (see Section 2 and the On-treatment Procedural Outline[s] specific to each FRACTION-RCC Sub-Protocol). Participants will be closely monitored for AEs and SAEs throughout the study. Blood and tumor tissue will be collected at specified times before and after study treatment administration for PK,

ADA, and pharmacodynamic analyses. Participants may withdraw or discontinue at any time based on criteria in Section 8.1.

5.1.1 FRACTION-RCC Tracks 1 and 2 Design

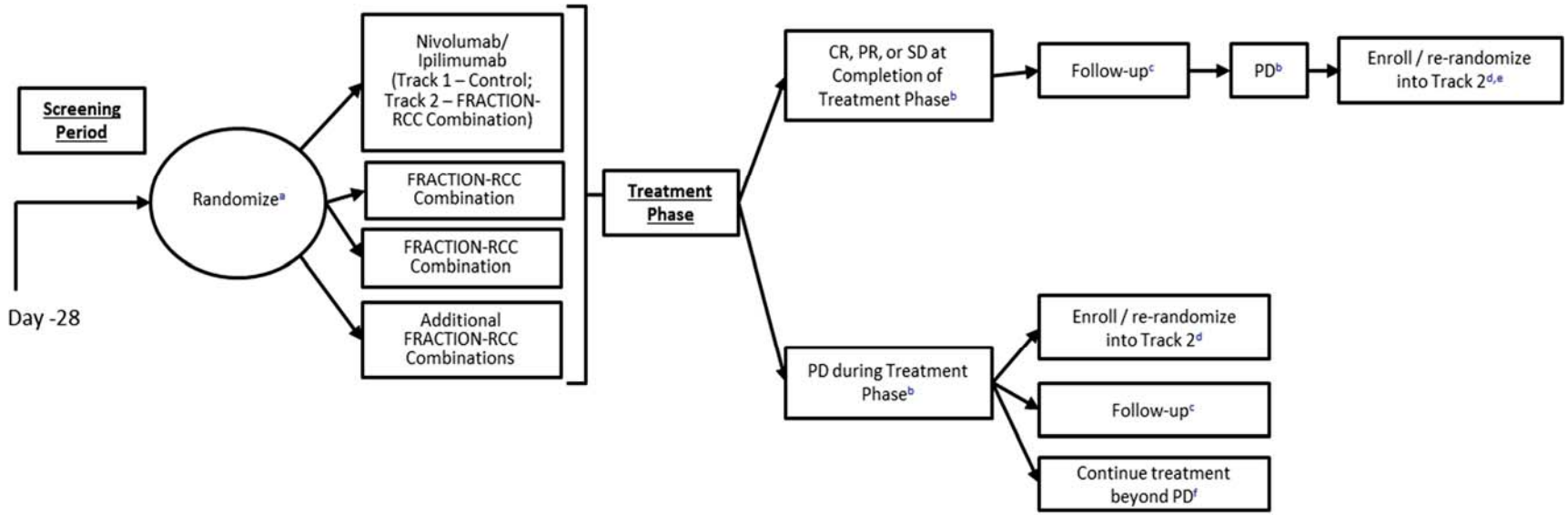
A detailed study schematic for both Tracks 1 and 2 is presented in Figure 5.1.1-1.

Participants who are naïve to anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment will be enrolled in Track 1, and they will be randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-RCC study treatment combinations. Randomization will be stratified by whether or not the participant has had prior TKI treatment. These participants will receive their assigned study treatment in Track 1 until completion of the Treatment Phase.

Participants who have received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment will be enrolled in Track 2 and randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-RCC study treatment combinations. In addition, participants with PD who were treated in Track 1 or 2 and continue to fulfill all entry criteria may be enrolled in Track 2 and re-randomized to a new combination other than that previously received, if applicable. These participants will receive their assigned study treatment in Track 2 until completion of the Treatment Phase. The number of participants who initially enroll in Track 2 and those who enroll in Track 2 after treatment on Tracks 1 or 2 is described in Section 10.1.

- **Participants with CR, PR, or SD** at the end of 2 years on Track 1 or 2 Treatment Phase will:
  - Enter study safety follow-up (FU) and complete FU1, FU2, and FU3 visits
- **Participants with PD** during the Track 1 or 2 Treatment Phase will:
  - Enter study follow-up (Not applicable per Protocol Amendment 07)
  - Enter (or re-enter) Track 2, if eligible and if a new study treatment combination is available, and be randomized to a new combination. (Re-randomization is no longer applicable per Protocol Amendment 07)
  - Continue treatment beyond progression if criteria in Section 7.4.2 are met. (Not applicable per Protocol Amendment 07)
  - Enter safety follow-up and complete FU1, FU2, and FU3 visits.
- **Participants with CR, PR, or SD <u>who enter study follow-up and subsequently progress</u>** will:
  - Enter (or re-enter) Track 2, if eligible and if a new study treatment combination is available, and be randomized to a new combination. (Re-randomization is no longer applicable per Protocol Amendment 07)
  - Enter safety follow-up and complete FU1, FU2, and FU3 visits

Figure 5.1.1-1: Tracks 1 and 2 Study Design Schematic



Note: This diagram presents the protocol-mandated treatment flow for Tracks 1 and 2, including re-entry into Track 2. Alternatives must be discussed with the BMS Medical Monitor (or designee).

[a] For Track 1, stratify by TKI treatment.

[b] CR, PR, SD, and PD as defined by RECIST v1.1. Assessments of PR and CR must be confirmed at least 4 weeks later following initial assessment.

[c] Safety Follow-up Phase

[d] Not applicable per Protocol Amendment 07: If participants are eligible and if a new study treatment combination is available, they can enroll/re-randomize to a new combination.

[e] Not applicable per Protocol Amendment 07: Each individual participant may receive multiple study treatments, including initial treatment, treatment beyond investigator-assessed progression, and/or entry into Track 2, assuming that the participant continues to fulfill all eligibility criteria at each new randomization point (see Section 5.1.3.3 for details).

[f] Not applicable per Protocol Amendment 07: Participants with PD during treatment may continue treatment beyond progression up to 2 years if criteria in Section 7.4.2 are met.

Abbreviations: CR = complete response; FRACTION = Fast Real-time Assessment of Combination Therapy in Immuno-Oncology; PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

5.1.2 Safety Monitoring Board and Other External Committees

Two independent committees may be utilized: a Safety Monitoring Board (SMB) and an Independent Review Committee (IRC).

The SMB will be established to provide safety monitoring and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The SMB will meet at least twice per year concurrent with BMS internal continuous safety assessments. If needed, additional ad hoc SMB meetings may be convened. Safety-related data summaries and listings (by study Track and study treatment arm as appropriate) will be provided to SMB to facilitate safety monitoring. The SMB will act in an advisory capacity to BMS and will monitor participant safety throughout the study. Additional details are provided in the SMB Charter.

The IRC may be established at the discretion of the Sponsor. The IRC may review all available tumor assessment scans to determine response (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria). IRC-determined response may be used in the analyses of ORR, progression-free survival rate (PFSR), and duration of response (DOR).

5.1.3 Study Phases

Participants will complete up to 3 phases of the study: Screening, Treatment, and Safety Follow-up.

5.1.3.1 Screening

Prior to screening for the protocol, investigative sites are required to determine if a participant has previously received anti-PD-1, anti-PD-L1, anti-CTLA-4, or TKI treatment through their Institutional database, participant medical history, or Institutional prescreening process. Once determined, treatment experience is considered source data for this FRACTION-RCC study. The participant must be provided with the FRACTION-RCC study Institutional Review Board (IRB)-approved written consent. Once the consent is signed, the participant is then considered to have entered screening. The treatment status must be entered into the enrollment management system, and participants will be required to submit a fresh tumor biopsy to the central laboratory. An adequate baseline tumor biopsy (as determined by a central laboratory pathologist or a local pathologist) must be obtained prior to randomization.

The Screening Phase for each Track will last for up to 28 days. Participants will be enrolled using Interactive Response Technology (IRT).

If a participant surpasses the 28-day window during the Screening Phase due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting time for a study-related laboratory value), the participant must be re-consented but does not need to be assigned a new participant identification number. To reduce any undue burden of procedure in this participant population in this situation, the amount of repeat procedures from the initial screening will be minimized while maintaining safety and eligibility under the discretion of the BMS Medical Monitor (or designee) and investigator.

Enrollment in all study treatment arms in each Track will be competitive.

5.1.3.2 Treatment

The details of the Treatment Phase duration are provided in Section 5.1. Further details of the study treatment administration are in each FRACTION-RCC Sub-Protocol. Study assessments are to be collected as outlined in the On-treatment Procedural Outline(s) in each FRACTION-RCC Sub-Protocol.

Assessment of response will be outlined for each combination therapy in the specific FRACTION-RCC Sub-Protocol. Assessments of PR and CR must be confirmed at least 4 weeks later following initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (see Appendix 5).

Participants will generally be allowed to continue study treatment until the first occurrence of one of the following: 1) completion of approximately 2 years of study treatment, 2) PD 3) clinical deterioration suggesting that no further benefit from study treatment is likely, 4) intolerable toxicity, 5) the meeting of criteria for discontinuation of study treatment, as outlined in Section 8.1. Individual participants with confirmed CR will be given the option to discontinue study treatment on a case-by-case basis after specific consultation and agreement between the investigator and the BMS Medical Monitor (or designee) in settings where the benefit/risk ratio justifies discontinuation of study treatment.

All participants will be treated as per Section 5.1, unless criteria for study treatment discontinuation are met earlier (Section 8.1 in the FRACTION-RCC Master Protocol and Section 8.1 in the FRACTION-RCC Sub-Protocol). Upon completion of the Treatment Phase, all participants will enter the Safety Follow-up Phase (see Section 5.1.3.3 and Table 2-3).

As of Protocol Amendment 07, collection of blood or other biological samples for reasons other than safety monitoring (eg, PK, ADA, biomarkers, etc) should be discontinued. Please refer to Table 2-3 and Sections 9.5, 9.6, and 9.8.

5.1.3.3 Follow-up

As of Protocol Amendment 07, tumor scans, survival status follow-up, and collection of subsequent treatment information will end once the participant has disease progression or treatment discontinuation for any reason, whichever occurs first. Any assessments for monitoring of safety will continue per protocol until the final follow-up visit (FU3). Please refer to Table 2-3.

Safety Follow-up

Upon completion of the Treatment Phase, all participants will enter the Safety Follow-up Phase once the decision is made to discontinue the participant from study treatment (eg, at EOT).

For participants that complete all scheduled weeks of study treatment, EOT visit will be the same as the last scheduled and completed On-treatment visit and the start of Week 1 safety follow-up visit. For participants that do not complete all scheduled weeks of study treatment, EOT visit will be the most recent On-treatment visit (with all available safety and response data; does not need to be repeated) and will be considered the start of Week 1 safety follow-up visit.

After the EOT visit, all participants will be evaluated for any new AEs until 100 days following the last dose of study treatment, as specified in each FRACTION-RCC Sub-Protocol. All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days) after the last dose of study treatment or coinciding with the date of discontinuation (± 7 days), if the date of discontinuation is greater than 30 days after the last dose, to monitor for AEs. All participants will be required to complete the 3 clinical safety follow-up visits, regardless of whether they start a new anti-cancer treatment, except for those participants who withdraw consent for study participation or those participants who are re-randomized into Track 2.

5.2 Number of Participants

In Track 1, up to 63 anti-PD-1/PD-L1 or anti-CTLA-4 treatment-naive participants will be treated per study treatment combination. In Track 2, up to 41 participants will be treated per study treatment combination. See Section 10.1 for details.

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.

5.4 Scientific Rationale for Study Design

BMS has an extensive portfolio of novel agents that span a variety of targets. To determine which combinations show the most clinical promise and thus should be prioritized for future registrational studies, BMS has initiated the FRACTION Program. The FRACTION Program will treat participants with different study treatment options and employ repeat blood sampling, tumor biopsies, and serial assessments to understand markers of response to treatment. These approaches are supported by various precedent studies that use innovative trial designs to quickly assess new agents in participants with the goal of reducing the time and number of participants required to bring these treatments to those who will benefit from them. For the FRACTION Program, specific study treatment combinations and/or control treatments will be introduced in FRACTION Sub-Protocols for each FRACTION study. Study treatment combinations that have high potential to produce transformational activity in the cancer compared to the control, based on both preclinical and early clinical trials data, will be selected. See Section 3.1 for details.

5.4.1 Rationale for Duration of Therapy

The optimal duration of immunotherapy is an important question and continues to be investigated. In Study CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among the 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-

randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[50]

Moreover, accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. In study CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[51] These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16% to 18% for squamous and non-squamous NSCLC respectively).[52]

Taken together, the data suggest a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. Also, treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

Collectively, these data suggest that there is minimal, if any, benefit derived from continuing IO treatment beyond 2 years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in study CA018005, treatment with BMS-986217 and nivolumab will be extended for up to 2 years in this study.

5.5 Justification for Dose

Please refer to individual FRACTION-RCC Sub-Protocols for their respective dose justifications.

6 STUDY POPULATION

For entry into the FRACTION-RCC study (per FRACTION-RCC Master Protocol), the following criteria MUST be met prior to dosing on Day 1. For entry into a study treatment per a FRACTION-RCC Sub-Protocol, additional treatment-specific criteria, if applicable, must also be met.

No exceptions will be granted.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must be able to give self-consent and then sign and date an IRB/Independent Ethics Committee (IEC)-approved written informed consent in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not considered part of normal patient care.

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

c) Participants must provide consent for 3 mandatory tumor biopsy samples (as detailed in "2)j)" below).

2) Type of Participant and Target Disease Characteristics

a) All participants must have advanced (not amenable to curative surgery or radiation treatment) or metastatic (American Joint Committee on Cancer Stage IV) RCC

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

c) Prior adjuvant or neoadjuvant treatment with IL-2, INFα, or radiotherapy is permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 4 weeks prior to randomization.

d) Prior treatment with targeted agents such as TKIs or antiangiogenic monoclonal antibodies are eligible.

e) Track-specific eligibility criteria

i) Track 1: anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment-naïve participants

(1) Participants must not have received any anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment, prior to this study. Participants previously treated with agents other than anti-PD-1, anti-PD-L1, or anti-CTLA-4 are eligible for Track 1.

(2) Participants may have had prior treatment for progressive or recurrent disease.

(a) Participants who have received IL-2 or INFα are eligible.

(b) Participants may have received targeted treatment (see above)

(3) Not applicable per Amendment 02.

(4) After signing informed consent, participants will be required to submit a fresh tumor biopsy prior to treatment as described below [see "6.1.2)j)"]. Participants must have an adequate tumor biopsy (as determined by a central laboratory pathologist or a local pathologist) prior to randomization.

(5) Participants must be evaluated for risk of the disease as defined by International Metastatic RCC Database Consortium (IMDC) score. (Appendix 8).

(6) Based on the results from CheckMate-214[53], participants with favorable risk profile by IMDC Score must have been treated with sunitinib prior to randomization into Track 1 nivolumab plus ipilimumab.

(7) Karnofsky Performance Status (KPS) must be ≥ 70% (Appendix 7).

ii) Track 2: anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment-experienced participants

(1) Participants must have had progressive or recurrent disease during or after anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment. (Participants treated with any study treatment targeting PD-1, PD-L1, or CTLA-4 will be considered anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experienced, respectively.)

(2) Participants who have had prior treatment with any of the agents (or any other agent targeting PD-1, PD-L1, or CTLA-4) in monotherapy or in any combination regimen in a FRACTION-RCC Sub-Protocol are eligible for treatment on Track 2.

(3) Participants who have had prior combination treatment with the same combination agents (or IO agents directed against the same targets) as 1 of the combination regimens in a FRACTION-RCC Sub-Protocol are eligible for study treatment on Track 2 but must be randomized to another combination regimen (as outlined in Section 5.1.1 Inclusion Criteria of each FRACTION-RCC Sub-Protocol).

(4) Participants may have received targeted treatment (see above).

(5) After signing informed consent, participants will be required to submit a fresh tumor biopsy prior to treatment as described below [see "6.1.2)j)"]. Eligibility will not be determined by this biopsy.

f) At the time of screening, participants must have a life expectancy of at least 3 months following their most recent chemotherapy or immunotherapy for entry into all Tracks.

i) Participants who wish to be re-randomized to a new study treatment combination in Track 2 following progression on a prior study treatment in Tracks 1 or 2 must have a life expectancy of at least 3 months following the last study treatment.

g) Participants receiving prior palliative radiotherapy to a non-central nervous system (CNS) lesion must have completed that treatment at least 2 weeks prior to the first dose of study treatment.

i) Participants with symptomatic tumor lesions at baseline who may require palliative radiotherapy within 4 weeks of the first dose of study treatment are strongly encouraged to receive palliative radiotherapy prior to enrollment, and they must complete that treatment at least 2 weeks prior to the first dose of study treatment.

h) Participants must have at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for solid tumors response assessment (see Appendix 5).

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

i) Participants with toxicity from any prior anti-cancer treatment must have their toxicity returned to Grade ≤ 1 (NCI CTCAE Version 4.03) or baseline before administration of study treatment.

i) Participants with Grade ≥ 2 toxicities attributed to prior anti-cancer treatment that are not expected to resolve and result in long-lasting sequelae, such as neuropathy after a platinum-based treatment, are eligible.

ii) Grade >1 alopecia or fatigue is permitted.

j) Participants must allow a tumor biopsy at the following time points: 1) baseline (prior to study treatment); 2) on-study (Day 28 On-treatment); and 3) EOT, defined as at the time of progression or at the time of a clinically significant event (eg, at EOT for participants with PR or SD or at EOT for participants who discontinue treatment due to an AE) provided that the biopsy is at acceptable clinical risk as judged by the investigator for each study treatment regimen to 1) identify predictive biomarkers for both safety and efficacy of a given combination, 2) define the mechanism of action for a particular combination (pharmacodynamic assessment), and 3) determine the mechanisms of resistance to a particular combination.
   i) Participants who do not have accessible or suitable lesions are not eligible.
      (1) Baseline biopsies may be collected from participants with a single measurable lesion (primary or metastatic), as long as it is not an excisional biopsy.
   ii) For participants whose pretreatment biopsy yields inadequate tissue quantity or quality (as determined by a pathologist in the central or local laboratory), re-biopsy is permitted.
   iii) The solid tumor tissue specimen must be a core-needle biopsy or an excisional or incisional biopsy. Fine-needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.
   iv) The biopsy at progression of disease after treatment on any Track may function as the pretreatment biopsy for subsequent treatment on Track 2.

k) Study personnel must ensure that the archival tissue block (preferred) or slides samples, if available, are located and shipped to the central laboratory prior to randomization within 6 weeks of signing the written informed consent, as long as this tissue will not be used for the screening biopsy sample.

l) Participants must have adequate organ function, as defined by the following:
   i) White blood cells ≥ 2,000/μL (stable off any growth factor after discontinuation within 2 weeks of the first study treatment administration)
   ii) Neutrophils ≥ 1,500/μL (stable off any growth factor after discontinuation within 2 weeks of the first study treatment administration)
   iii) Not applicable per Amendment 02
   iv) Not applicable per Amendment 03
   v) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3× institutional upper limit of normal (ULN)
   vi) Total bilirubin ≤ 1.5× institutional ULN (except for participants with Gilbert's syndrome who must have normal direct bilirubin)

vii) Serum creatinine ≤ 1.5× institutional ULN or creatinine clearance (CrCl) > 40 mL/min (measured using the Cockcroft-Gault formula below):

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

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

i) Platelets ≥ $100 \times 10^3/\mu L$ (transfusion to achieve this level is not permitted within 4 weeks of the first study treatment administration)

ii) Hemoglobin ≥ 9.0 g/dL (transfusion to achieve this level is not permitted within 4 weeks of the first study treatment administration)

m) Participants must be able to comply with restrictions and prohibited activities/treatments listed in Section 7.7.1.

n) Participant re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (eg, participant has not been treated). If re-enrolled, the participant must be re-consented.

3) Age and Reproductive Status

4) In addition to the reproductive guidelines noted below, please refer to the individual sub-protocol for additional requirements regarding reproductive guidelines.

a) Males and females, ages 18 years or age of majority or older at the time of consent

b) Women of child-bearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus the time required for the study treatment to undergo approximately 5 half-lives, plus the duration of 1 ovulatory cycle (30 days) for a total of 5 months posttreatment completion (see Appendix 4). If the half-life of a study treatment in a FRACTION-RCC Sub-Protocol is longer than approximately 5 half-lives of nivolumab, this will be addressed in the FRACTION-RCC Sub-Protocol.

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

f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (see Appendix 4) for the duration of treatment with study treatment(s) plus approximately 5 half-lives of the study treatment, plus the duration of sperm turnover (90 days), for a total of 7 months posttreatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

g) Azoospermic males are exempt from contraceptive requirements.

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) Participants must not have suspected, known, or progressive CNS metastases; have untreated CNS metastases; or have the CNS as the only site of disease.

i) Participants are eligible if CNS metastases are adequately treated and participants neurologically return to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to study entry. In addition, participants must be either off corticosteroids or on a stable or decreasing dose of prednisone ≤ 10 mg daily (or equivalent) for at least 2 weeks prior to study entry.

ii) Participants must not have leptomeningeal disease or carcinomatous meningitis.

b) Participants must not have prior malignancy active within the previous 3 years, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

c) Participants must not have other active malignancy requiring concurrent intervention.

d) Participants must not have received a prior organ allograft.

e) Participants must not have received any anti-cancer treatment (eg, chemotherapy, radiotherapy [except for palliative radiotherapy, which can be received up to 2 weeks prior to study treatment]; biologics; or immunotherapies, including investigational treatments) within 4 weeks prior to the first dose of study treatment administration.

i) Participants who have received noncytotoxic anti-cancer therapies (eg, prior use of targeted treatment or hormonal treatment) and who completed treatment at least 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of study treatment are eligible to enroll. However, if 5 half-lives is shorter than 4 weeks, agreement with the BMS Medical Monitor (or designee) is mandatory.

f) Participants must not have active, known, or suspected autoimmune disease.

i) Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement treatment, 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.

ii) Participants must not have uncontrolled adrenal insufficiency.

g) Participants must not have a condition requiring systemic treatment with either corticosteroids (prednisone > 10 mg daily or equivalent) or other immunosuppressive medications within 14 days of study treatment administration.

i) Inhaled or topical steroids and adrenal replacement steroid (prednisone > 10 mg daily or equivalent) are permitted in the absence of active autoimmune disease.

h) Participants must not have a history of life-threatening toxicity related to prior IO treatment (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or treatment specifically targeting T-cell co-stimulation or immune checkpoint pathways).

   i) Participants with toxicities that are unlikely to recur with standard countermeasures (eg, hormone replacement treatment after adrenal crisis) are eligible.

i) Participants must not have interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

j) Participants must not have uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

   i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

   ii) Uncontrolled angina within the past 3 months

   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

   iv) QT interval corrected with Fridericia's formula ≥ 480 ms

   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, myocarditis, pericarditis, or significant pericardial effusion)

k) Participants who require daily supplemental oxygen treatment are excluded.

l) Participants must not have any positive test result for hepatitis B virus or hepatitis C virus (HCV) indicating presence of virus, eg, hepatitis B surface antigen (Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-ribonucleic acid [RNA] negative).

   i) Participants with a history of resolved hepatitis A virus infection are eligible.

m) Participants must not have evidence of active infection requiring antibacterial, antifungal, or antiviral treatment ≤ 7 days prior to initiation of study treatment.

n) Participants must not have a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

   i) Testing for HIV must be performed at sites mandated by local requirements.

o) Participants must not have known or suspected active tuberculosis.

p) Participant must not have had any major surgery (eg, nephrectomy) within 4 weeks of study treatment administration. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

q) Participants must not have received nononcology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to the first dose of study treatment.

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

r) Participants must not have received packed red blood cell or platelet transfusion within 4 weeks prior to the first dose of study treatment.

s) Participants must not have a known or underlying serious or uncontrolled medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study.

2) Allergies and Adverse Drug Reaction

a) History of any significant treatment allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune-modulating therapies (eg, checkpoint inhibitors and T-cell co-stimulatory antibodies).

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

3) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials 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

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

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

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

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

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and is described in each FRACTION-RCC Sub-Protocol.

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

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

7.1 Treatments Administered

Other treatments administered as part of the study that are critical to claims of efficacy (eg, background treatment, rescue medications) will be considered study treatment. A table describing the study treatments and dosage information is provided in each FRACTION-RCC Sub-Protocol.

7.2 Method of Treatment Assignment

This is an open-label study. All participants will be centrally randomized using an IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Specific study treatments are listed in each FRACTION- RCC Sub-Protocol. Study treatment will be dispensed at the study visits as listed in the On-treatment Procedural Outline(s) in each FRACTION-RCC Sub-Protocol.

All participants must be assigned a patient identification number (PID) upon providing a signed IRB/IEC-approved written informed consent. During the screening visit, the investigative site will utilize the IRT for enrollment and receive a 5-digit PID designated by BMS that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential PIDs starting with 00001 (eg, 00001, 00002, 00003...00010). The PID will ultimately be composed of the site number and participant number. For example, the first participant screened (eg, enrolled) at Site Number 1 will have a PID of 0001-00001. The following information is required for enrollment:

- Date of obtaining informed consent
- Date of birth
- Gender at birth
- Anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experience (see Section 5.1.3.1)

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

- Participant number
- Date of birth

Randomization participant schedules will be generated and maintained by the IRT vendor. At the conclusion of the trials, BMS will receive copies of all generated participant schedules from the vendor. Because of the nature of the study design, limited early access to the randomization information will be granted to the study team to facilitate early analyses for internal decision making (early termination of study treatment arm, etc).

Each participant who is randomized will be assigned a unique randomization number. This is not the primary identifier for the participant but used for the randomization schedule. The primary identifier will be the PID described above, for use on the case report form (CRF) and source documents. A participant being re-randomized in Track 2 will be assigned a different randomization number but will retain the same PID. Randomization numbers will be assigned using a Central Randomization System in the order in which participants qualify for study treatment, not in the order of study enrollment. Randomization ratios within each Track will be specified in each FRACTION-RCC Sub-Protocol. If, within a given Track, study treatment arms from more than 1 FRACTION-RCC Sub-Protocol within the FRACTION-RCC Master Protocol are simultaneously open to enrollment, then a new participant could be assigned to any of the open study treatment arms. In Track 1, randomization of participants will be stratified by whether or not the participant has had prior TKI treatment. In Track 1, participants will be randomized to newly added study treatment arms/study treatments (through FRACTION-RCC Sub-Protocols) in a ratio as specified in each new FRACTION-RCC Sub-Protocol. New randomization schedules for new FRACTION-RCC Sub-Protocols will be generated. If accrual for current FRACTION-RCC Sub-Protocols is still ongoing, participants will be allocated to the existing randomization schedule or new randomization schedule based on a prespecified allocation ratio. Details of allocation ratio will be specified in the new FRACTION-RCC Sub-Protocol. In Track 2, participants will be randomized to existing study treatment arm/study treatments and newly added study arm/study treatments with equal probability.

Prespecified study treatment arm caps (according to Simon 2-stage [optimal] design) will be utilized to control the accrual for each combination study treatment arm under different Tracks (Tracks 1 and 2). The cap for the nivolumab in combination with ipilimumab control arm under Track 1 will be set equal to the largest cap among its corresponding experimental arms. In the event that 1 or more participants go off study without being evaluable for response (ie, with no postbaseline tumor measurements and no evidence of clinical progression or death due to disease

progression), the enrollment cap for that study treatment arm may be correspondingly raised if needed to ensure that a sufficient number of evaluable participants are available for decision making according to the Simon 2-stage (optimal) design. If the decision is made to close any study treatment arm for safety concerns, the cap for that study treatment arm will be reduced to the current number of participants already randomized. Accrual will be stopped immediately. Enrollment caps to Track 2 based on new participants or re-randomized participants are described in Section 10.1.2.

Specific instructions for randomization into the Central Randomization System will be provided in a separate manual.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dosage Modification

Specific dosing and treatment regimens for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are outlined in each FRACTION-RCC Sub-Protocol.

7.4.1 Dose Reductions and Delays and Criteria to Resume Dosing

Tumor assessments for all participants should continue as per protocol **even if dosing is delayed**.

Guidelines for dose reductions and delays due to toxicity and for resuming study treatment for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are provided in each FRACTION-RCC Sub-Protocol.

7.4.2 Treatment Beyond Disease Progression

Accumulating evidence indicates that a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[54]

Participants will be permitted to continue on study treatment beyond initial RECIST v1.1-defined PD as long as they meet the following criteria:

- Participant had investigator-assessed clinical benefit.
- Participant continues to meet relevant eligibility criteria, as determined by the BMS Medical Monitor (or designee) in discussion with the investigator.
- Participant has stable performance status.
- Participant is tolerating study treatment.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

The decision to continue study treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor (or designee) and documented in the study records.

A follow-up scan should be performed at the next scheduled imaging evaluation (per the FRACTION-RCC Sub-Protocol) (but no sooner than 6 weeks) to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment. If the investigator feels that the participant continues to achieve clinical benefit by continuing study treatment, the participant should remain on the study and continue to receive monitoring according to the On-treatment Procedural Outline specific to each FRACTION-RCC Sub-Protocol.

For participants who continue study treatment beyond initial RECIST v1.1-defined PD, further progression is defined as an additional 10% increase in tumor burden volume with a minimum 5 mm absolute increase from time of initial PD assessment. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered nonmeasurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm. Study treatment should be discontinued in any participant for whom these criteria are met and should be documented.

Not applicable per Protocol Amendment 07.

7.4.3 Management Algorithms for IO and Oncology Agents

IO agents are associated with adverse events (AE)s that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab, ipilimumab, and their combination to assist investigators in assessing and managing the following groups of AEs:

- Pulmonary
- Gastrointestinal
- Hepatic
- Endocrinopathies
- Renal
- Skin
- Neurological

The clinical nature of AEs noted with each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab will determine the role of the algorithms above for use in toxicities related to its use in this study.

The management algorithms recommended for utilization for IO and non-IO agents are included in Appendix 6 and in each FRACTION-RCC Sub-Protocol, if not currently in the master protocol.

7.4.4 Treatment of Treatment-related Infusion Reactions

Treatment of study treatment-related infusion reactions for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab is provided in each FRACTION-RCC Sub-Protocol.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

For study treatments not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label. Infusion-related supplies (eg, intravenous bags, in-line filters, 0.9% NaCl solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

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

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by treatment accountability, as well as by recording administration of each study treatment in the participants' medical records and CRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following prohibitions and restrictions apply to all FRACTION-RCC Sub-Protocols for the FRACTION-RCC study. Additional FRACTION-RCC Sub-Protocol-specific prohibitions and/or restrictions are outlined in each FRACTION-RCC Sub-Protocol.

The following medications are prohibited during the Treatment Phase of the study:

- Immunosuppressive agents (except for those stated in Section 7.7.3) are prohibited, unless they are utilized to treat an AE.
- Chronic systemic corticosteroids (prednisone > 10 mg daily or equivalent; except for those stated in Section 7.7.3) are prohibited, unless they are utilized to treat an AE.
- Vaccines (except for those stated in Section 7.7.3) are prohibited.
- Any medicinal herbal preparations within 2 weeks prior to the first dose of study treatment, are prohibited unless prescribed by a treating physician. Use of marijuana and its derivatives for treatment of symptoms related to cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Any concurrent anti-neoplastic treatment (ie, chemotherapy; immunotherapy; extensive, nonpalliative radiation treatment; or standard or investigational agents for treatment of RCC) is prohibited other than those included in the study treatment combinations.

Any concomitant therapies must be recorded on the CRF from screening to follow-up.

7.7.2 Other Restrictions and Precautions

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and, if so, what type and dose of contrast are appropriate. Magnetic resonance imaging (MRI) contrast should not be given to participants with severe renal insufficiency (eg, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) because of increased risk of nephrogenic systemic fibrosis in this participant population. In these participants, alternative imaging tests or MRI without gadolinium should be considered. In addition, participants are excluded from MRI if they have tattoos, metallic implants, or pacemakers, etc. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and the standard set by the local IRB/IEC.

7.7.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses of prednisone > 10 mg daily are permitted. A brief course (less than 3 weeks) of corticosteroids

prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

- Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the participant is on a stable dose) and adrenal replacement steroid doses of prednisone > 10 mg daily or equivalent are permitted in the absence of active autoimmune disease. Nonabsorbed intra-articular steroid injections will be permitted.
- Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Participants receiving corticosteroids must be at prednisone ≤ 10 mg/day or equivalent prior to re-initiation of study treatment. Participants may continue to receive hormone replacement treatment.
- The inactivated seasonal influenza vaccine can be given to participants while on treatment without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (ie, Pneumovax®, varicella vaccine, etc) may be permitted but must be discussed with the BMS Medical Monitor (or designee) and may require a study treatment washout period prior to and after administration of the vaccine.
- Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving investigational agents is unknown.

7.7.4 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the study. Limited radiation treatment or surgery to control isolated lesions is permitted for participants who have investigator-assessed clinical benefit following consultation with the BMS Medical Monitor (or designee).

Participants should not receive study treatment during radiation because the potential for overlapping toxicities with radiotherapy and FRACTION-RCC study treatment combinations or nivolumab in combination with ipilimumab is not known. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then study treatment administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Participants receiving palliative radiation of target lesions will have the evaluation of ORR just prior to

radiotherapy, but these participants will no longer be evaluable for the determination of response subsequent to the date palliative radiation occurs.

For participants who need to undergo elective surgery (not tumor related) during the study, it is recommended to hold study treatment(s) for at least 2 weeks before and 2 weeks after surgery or until the participant recovers from the procedure, whichever is longer. Prior to resuming study treatment, surgically related AEs should resolve to ≤ Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

7.7.5 Supportive Care Management

Supportive care management for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab, as necessary, is outlined in each FRACTION-RCC Sub-Protocol.

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures as outlined in Section 2. The only exception to this is when a participant specifically withdraws consent for any further contact with him or 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for the treatment of either a psychiatric or a physical (eg, infectious disease) illness
- Inability to comply with the protocol
- Pregnancy
- Documented disease progression as defined by RECIST v1.1 (see Appendix 5), unless the participant meets criteria for treatment beyond progression (see Section 7.4.2) or the participant continues study treatment by entering another Track (Section 5.1.3.3)

- Clinical deterioration while receiving active study treatment that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Discretion of the investigator
- Protocol-defined reasons for discontinuation (Criteria for permanent discontinuation for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are provided in each FRACTION-RCC Sub-Protocol.)
- End of study

Refer to Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations that can be completed.

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

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

Additional study treatment-specific discontinuation criteria are provided in each FRACTION-RCC Sub-Protocol.

8.1.1 Permanent Discontinuation

Criteria for permanent discontinuation for each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab are provided in each FRACTION-RCC Sub-Protocol.

8.1.2 Study Treatment Combination Arm Discontinuation Criteria

In the event that 20% or more of study participants in a novel FRACTION-RCC study treatment combination arm of a given Track, at any given time, meet any of the toxicity criteria for permanent discontinuation (as described in Section 8.1), then consideration will be given to discontinue that FRACTION-RCC study treatment combination arm in that Track. This will include early side effects seen with combination agents and longer-term effects such as endocrinopathies. This action will be taken in consultation with the SMB and will consider other pertinent facts in coming to a

decision, including the toxicity profile of that combination seen outside FRACTION-RCC, participant benefit as measured by anti-tumor response, and comparison to nivolumab in combination with ipilimumab.

Discontinuation of a study treatment combination arm in a given Track for any reason WILL NOT lead to discontinuation for that combination in all Tracks. Safety of all open-label study treatment combination arms in other Tracks that contain the same agent (or agents) will be assessed by SMB and the Sponsor. In the event of serious, unexpected, or life-threatening emergent toxicities, relevant study treatment combination arms may then be modified to maintain the safety of participants. Decisions on such steps and the re-initiation of any study treatment combination arms that had been stopped would be made by SMB in consultation with the Sponsor and relevant authorities (eg, IRB/IEC).

8.1.3 Post Study Treatment Study Follow-up

In this study, PFSR 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 safety (Section 5).

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 or 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 posttreatment study follow-up, and entered onto the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol.
- 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 study treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided that the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol.

9.1 Efficacy Assessments

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

CT scans should be acquired with 5-mm slices with no intervening gap (contiguous). Should a participant have a contraindication for CT intravenous contrast, a contrast-enhanced MRI of the chest, abdomen, pelvis, and other known sites of disease may be obtained. MRIs should be acquired with slice thickness of 5 mm with no gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.

MRI or CT brain scans during on-study treatment and follow-up periods are required only if clinically indicated for new signs and symptoms that suggest CNS involvement. Participants with a history of bone metastasis should have a bone scan, if clinically indicated. All participants should receive scans at FU1, except for participants with PD who started subsequent therapy or have already been treated beyond progression. Scans at FU3 will only be collected for patients with CR, PR, or SD at treatment discontinuation.

Assessments will be performed at baseline and at the time points described in each FRACTION-RCC Sub-Protocol up to and including Week 24 during the Treatment Phase or until disease progression per RECIST v1.1 criteria (see Appendix 5) or confirmed disease progression for participants treated beyond progression (defined as an additional 10% increase in tumor burden volume with a minimum 5 mm absolute increase from the time of initial PD assessment [an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD]), discontinuation of study treatment, or withdrawal from the study. Assessments will also be performed 30, 60, and 100 days after discontinuation of study treatment (ie, safety follow-up Visits 1; 2, and 3 for all participants). Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of response will be outlined for each combination therapy in the specific FRACTION-RCC Sub-Protocol. Assessments of PR and CR must be confirmed at least 4 weeks after initial response. Assessment of tumor response will be reported by the investigator for appropriate populations of participants, as defined by RECIST v1.1 criteria (see Appendix 5) for participants with solid tumors. Same modality/scanner should be used for all assessments.

Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST v1.1 criteria.[55] Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the CRF based on the investigator's assessment using RECIST v1.1 criteria. (See Appendix 5 and Section 7.4.2 for specifics of RECIST v1.1 criteria to be utilized in this study.)

Tumor assessments will be submitted to a third party radiology vendor on an ongoing basis; participant management is not dependent on third-party review of tumor assessments.

As participant's response to prior therapy is an important part of medical history, additional details regarding the previous therapy, including but not limited to best response to therapy, timing of progression on prior therapy, method of how the progression was measured, existence of confirmation scan to document progression and detailed information such as other clinical evidence (e.g., increased pain requiring palliative radiotherapy) to support progression, response/progression dates, and reason for discontinuation will be collected in this trial.

9.1.1 Imaging Assessment for the Study

Central assessments are not planned for this study; however, copies of all scans will be stored for possible future central analysis, if determined to be necessary by BMS. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

9.1.2 Patient-reported Outcomes

The effects of RCC and its treatment on health status and quality of life will be assessed using the 3-level version of the EQ-5D self-report questionnaire (EQ-5D-3L) and the Functional Assessment of Cancer Therapy-Kidney Symptom Index-disease related symptoms (FKSI-DRS).[56,57] Participants will be asked to complete the EQ-5D-3L and FKSI-DRS during on-study clinic visits and during safety follow-up. The questionnaires will be provided in the participant's preferred language if available and may be administered by telephone. A standardized script will be used to facilitate telephone administration of the EQ-5D. A similar script does not exist for the FSKI-DRS, though participants will be provided with a hard copy of the questionnaire to take home and use as a visual aid during telephone interviews. For those patients not able to vocalize the questionnaire response over the phone, they can complete it via pen and paper (initial and date each page) and mail or email to the site. Section 2 and the On-treatment Procedural Outline(s) in each FRACTION-RCC Sub-Protocol provide information regarding the timing of patient-reported outcomes assessments.

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

The FKSI-DRS is a 9-item index of the most important symptoms associated with kidney cancer. The questionnaire was developed to accommodate the needs of clinical investigators interested in evaluating the efficacy and safety of new treatments or treatment combinations for advanced kidney cancer. The FKSI-DRS includes items measuring general symptoms (eg, pain, lack of energy, weight loss, bone pain, fatigue) as well as disease-related symptoms (eg, shortness of breath, coughing, fevers, blood in urine). Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). A summary score is derived by aggregating responses for the 9 items with higher scores indicating less symptom burden.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

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 and continue until 100 days following the last dose of study treatment, at the time points specified in the Schedule of Activities (see Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol). 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.

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

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). Participants who are randomized and never treated with study treatment must have SAEs collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment 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 the 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 or 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.

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

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

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (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 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 nonserious AEs of special interest (as defined in each FRACTION-RCC Sub-Protocol will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

The Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC, Food and Drug Administration, and Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the

appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to the BMS Medical Monitor (or designee). In order for the BMS Medical Monitor (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.

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

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

P-DILI is defined as follows:

1) Aminotransferase (AT) (ALT or AST) elevation > 3× ULN

AND

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

AND

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

The key responsibilities for investigators during p-DILI assessment include the following: (i) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for the following: (iii) timely evaluation and triaging of p-DILI cases, (iv) expedited reporting of p-DILI cases, and (v) expanded review of p-DILI cases, including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a Hepatic Laboratory Panel (ALT, AST, total bilirubin, and alkaline phosphatase). Any participant with an abnormal Hepatic Laboratory Panel that meets p-DILI criteria is a candidate for study treatment discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, nonexhaustively and by way of example only, infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as hepatocellular carcinoma), autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or

symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, 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 events meeting the definition of overdose must be reported as an AE/SAE (see Section Appendix 3).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol.

9.4.1 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. The clinical laboratory assessments are indicated in Table 9.4.1-1.

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

Results of all laboratory tests required by this protocol must be provided to BMS, recorded either on the laboratory pages of the CRF or by another mechanism, as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 9.2.6).

Table 9.4.1-1: Clinical Laboratory Assessments

Hematology	
CBC with differential including platelets	
Serum Chemistry	
AST	Total protein
ALT	Albumin
Total bilirubin	Sodium
Direct bilirubin	Potassium
Alkaline phosphatase	Chloride
LDH	Carbon dioxide or bicarbonate
Creatinine	Calcium

Table 9.4.1-1: Clinical Laboratory Assessments

BUN or urea	Phosphorus
Uric acid (screening only)	Magnesium
Glucose	Creatine kinase
Amylase	CrCl (screening only)
Lipase	C-reactive protein
Gamma-glutamyl transferase	
Urinalysis	
Protein	Leukocyte esterase
Glucose	Specific gravity
Blood	pH
Microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on the dipstick	
Serology	
Serum for Hepatitis A (IgG and IgM) antibody, Serum for hepatitis C antibody or hepatitis C RNA (if hepatitis C antibody is positive, reflex to hepatitis C RNA), hepatitis A, HBsAg, and HIV-1 and HIV-2 antibodies (Testing for HIV-1 and HIV-2 antibodies must be performed at the sites mandated by local requirements.)	
Other Analyses	
Pregnancy test (WOCBP only)	
TSH with reflex to free T3 and free T4, as applicable	
FSH, if needed to document postmenopausal status, as defined in Appendix 4	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CrCl = creatinine clearance; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of child-bearing potential.

9.4.2 Imaging Safety Assessment

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

9.5 Pharmacokinetics

Separate detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK samples will be provided in the Laboratory Procedures Manual.

The details pertaining to the timing of PK sample collection for Tracks 1 and 2, On-treatment and follow-up, are provided in each FRACTION-RCC Sub-Protocol.

The serum samples will be analyzed for study treatments. In addition, selected serum samples may be analyzed by an exploratory method that measures study treatment for technology exploration purposes; exploratory results will not be reported.

Upon implementation of Protocol Amendment 07, PK sample collection is no longer necessary for any participant who is on study treatment.

9.6 Pharmacodynamics

Pharmacodynamic measures (in the form of biomarker assessments) may be assessed for associations with clinical outcomes. There will be 3 types of specimens obtained for biomarker testing: whole blood, serum, and tumor tissue. The sample subtypes and testing plans associated with each are described in Section 9.8. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate Laboratory Procedures Manual.

Upon implementation of Protocol Amendment 07, samples for pharmacodynamic assessments are no longer necessary for any participant who is on study treatment.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Planned time points for all biomarker assessments are listed in the Schedule of Activities and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol.

Upon implementation of Protocol Amendment 07, samples for biomarker assessments (peripheral blood markers and tissue markers) are no longer necessary for any participant who is on study treatment.

9.8.1 Peripheral Blood Markers

9.8.1.1 Whole Blood Single Nucleotide Polymorphism and Genotyping

Whole blood will be collected from participants prior to study treatment initiation to generate genomic deoxyribonucleic acid (DNA) for candidate-based single nucleotide polymorphism genotyping analyses. These analyses will focus on single nucleotide polymorphisms within genes associated with or affecting immunoregulatory signaling to determine if natural variation within those genes is associated with a response to each component of each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab (and/or with AEs observed during treatment).

Additionally, genomic DNA from whole blood will be collected and may be used as a comparator for participants with tumors examined by whole exome or genome mutation analysis. Whole exome or whole genome sequencing methods may be used for this analysis.

Lastly, genomic DNA from whole blood will be collected and may be used for T-cell receptor sequencing.

9.8.1.2 Whole Blood for Peripheral Blood Mononuclear Cell-based Assays

Cytometry will be used to assess baseline and serial On-treatment alterations in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations obtained from all participants, as indicated in the On-treatment Procedural Outline(s)

in each FRACTION-RCC Sub-Protocol. Lymphocyte subsets to be assayed may include, but are not limited to, CD8+ and CD4+ T-cell subsets (activated, effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as GITR, human-leukocyte antigen-antigen D-related, PD-1, and/or intracellular IFNγ. NK cell populations will be monitored in a similar fashion, with a focus on characterizing subsets defined by the expression of activation markers (eg, NKG2D and IL-21R) and/or by markers that are associated with the potential of NK cells to lyse target cells (eg, CD107a, granzyme, and perforin).

Additional cytometry-based assays may focus on defining and monitoring the abundance of myeloid-derived suppressor cells, a cell type that appears to negatively impact immunologically-driven anti-tumor activity, which has been shown to be associated with poor prognosis in ipilimumab-treated participants.[58]

Lastly, assays may be completed to characterize the presence of T-cells directed against antigens present on tumors, including, but not limited to, over-expressed or virally associated factors such as EGFR, human papillomavirus, and cancer-testis antigen (NY-ESO1); T-cell receptor sequencing may also be performed using peripheral blood mononuclear cell samples. Detecting On-treatment increases in antigen-directed T-cells will provide evidence of adaptive immune responses against tumors and may be correlated with clinical outcomes.

9.8.1.3 Serum Factors

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and safety profile of each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be investigated by enzyme-linked immunosorbent assay (ELISA) and/or other relevant multiplex-based protein assay methods. Examples of specific analytes to be assessed may include, but are not limited to, factors induced by IFNγ signaling (eg, T-cell chemoattractants CXCL9 and CXCL10). Analyses may also focus on factors associated with prognosis and/or responses to standard therapeutic agents. In addition, soluble forms of receptors (eg, sPD-1 and s-GITR) and/or ligands (eg, sPD-L1 and s-GITRL) may be assessed.

Recent findings suggest that the presence of serum antibodies against melanoma-associated antigens may be predictive of response to immunotherapeutic agents such as ipilimumab.[59] To explore the possibility that the presence of autoantibodies is prognostic in other indications (and in response to each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab), baseline and On-treatment serum may be assessed for the presence and/or concentration of antibodies against specific antigens using ELISA and/or multiplex platform such as Invitrogen's ProtoArray®. Focus may be given on the detection of antibodies against proteins previously defined as tumor antigens, which are over-expressed in RCC. The presence of antibodies against viral antigens may also be monitored. Blood serum samples will be obtained, as indicated in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol.

MicroRNAs (miRNAs) may be evaluated from serum samples for association with response as potential prognostic markers.

9.8.1.4 Circulating Tumor DNA Analysis (Plasma Biomarkers)

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In patients with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 bp and specific genomic regions can be amplified with PCR. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma from patients with known driver mutations, BEAMing technology will be utilized to count the frequency of mutations in circulation.

9.8.2 Tissue Markers from Fresh Tumor Biopsies

9.8.2.1 Tissue Biopsies from Participants with RCC

Tracking changes in biomarkers measured in tumor tissue during treatment is instrumental in determining the mechanisms of action of cancer therapeutics. To monitor the presence (or absence) of infiltrating lymphocytes and to track other molecular changes within tumors in response to each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab, tumor biopsies will be collected, as outlined in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol. All participants must have tumor lesions that can be biopsied or collected via core needle, excisional, or incisional biopsy at acceptable clinical risk (as judged by the investigator) at baseline (pretreatment).

Sufficient tumor tissue must be obtained before initiation of study treatment from a primary or metastatic site. Tumor tissue samples must be shipped from site to central laboratory prior to randomization. Mandatory biopsies are required at the following time points: 1) baseline (prior to study treatment); 2) on-study (Day 28 within a collection window of Days 22 to 28); and 3) EOT, defined as at the time of progression or at the time of a clinically significant event (eg, at EOT for participants with PR or SD or at the EOT for participants who discontinue treatment due to an AE). Notify the BMS Medical Monitor (or designee) if the On-treatment or EOT biopsy may pose an unacceptable clinical risk.

Biopsied lesions should be distinct from index lesions being evaluated for radiological response (ie, participants must have at least 1 measurable tumor site by RECIST v1.1 criteria) marked for pretreatment and posttreatment radiological tumor assessments. Tumor sites marked for pretreatment and posttreatment radiological tumor assessment should be distinct from tumor sites being used for pretreatment and posttreatment biopsies, if at all possible. Biopsies must be excisional, incisional, or core-needle. Excisional biopsies are strongly encouraged where feasible. In circumstances when the participant has only 1 marker lesion (primary or metastatic), the baseline (pretreatment) biopsies from that lesion are acceptable but should not be excisional. Biopsies from previously irradiated lesions are only suitable if they subsequently progressed. Baseline samples may be obtained at any time following other screening procedures and prior to the first dose of study treatment. Archival specimens may not be substituted for fresh baseline

specimens but can be submitted to help understand the evolution of the tumor (ie, PD-L1 expression changes over time). The On-treatment biopsy may be obtained 28 days after the first dose of study treatment within a collection window of 7 days before that time point. The EOT biopsy may be done at the time of progression or at the time of a clinically significant event (eg, at EOT for participants with PR or SD or at the EOT for participants who discontinue treatment due to an AE). Participants must consent to biopsy procedures at baseline.

As described previously, complete instructions on the collection, processing, handling, and shipment of all biomarker specimens will be provided in a separate procedure manual. Refer to this manual for information pertaining to the collection and processing of tissue via biopsy or core needle. Collection procedures at baseline and on study treatment (and at progression) should be completed on a single, appropriately assessable lesion, when applicable. In case the lesion sampled at baseline is no longer accessible or within acceptable clinical risk to re-biopsy during the study (28 days after the first dose of study treatment on the Treatment Phase or at the end of the Treatment Phase), tissue from alternative lesion(s) may be obtained; this should be documented. Immediate confirmation for presence of viable tumor cells from collected tissue samples is strongly recommended. If adequate tissue is not obtained following initial passages of the needle, repeat passages may be completed.

Participants whose On-treatment biopsy yields inadequate tissue quantity or quality (lack of tumor) will be allowed to continue in the study and participate in the other biomarker assay collections (eg, blood collections) described in Section 2 and the On-treatment Procedural Outline(s) specific to each FRACTION-RCC Sub-Protocol. These participants are not exempt from future biopsy requirements at the time of PD or prior to randomization to a new study treatment combination arm and should be evaluated to assess if collection is feasible. Tumor tissue will be analyzed as described below. If tissue obtained from a large proportion of participants is deemed inadequate for testing (eg, possesses low tumor cell content), additional participants may be enrolled in an attempt to obtain tissue specimens that are better suited for testing.

9.8.2.2 Gene Expression Analyses

Exploratory analyses of messenger RNA (and/or miRNA) will be completed using total RNA isolated from fresh tumor tissue (processed in RNA later). RNA-sequencing, microarrays, and/or similar methodologies, including but not limited to quantitative real time polymerase chain reaction (PCR), will be used to assess gene expression patterns associated with RCC and to identify changes in those gene expression patterns following treatment with each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab, where applicable. Ultimately, this approach may lead to the identification of unique baseline or On-treatment RNA expression signatures that can be useful for identifying participants who are likely (or unlikely) to respond to treatment with a given FRACTION-RCC study treatment combination. Focus may be given to monitoring a battery of immunoregulatory genes associated with cancer cells or cancer-interacting lymphocytes. Examples within the latter group include genes associated with T-cells, NK cells, and/or IFNγ signaling. Such genes have been implicated previously in tumor responses.

9.8.2.3 Protein Expression and Mutation

A portion of the fresh biopsy specimen will be formalin fixed, paraffin embedded (FFPE), and analyzed by IHC to determine the abundance of immunoregulatory proteins present at the tumor site. Such analyses may reflect the presence of tumor-infiltrating immune cells or the expression of immunoregulatory proteins by the tumor and/or surrounding stroma. Analytes may include, but are not limited to, CD3, CD4, CD8, FoxP3, GITR, GITR ligand, PD-L1, and components of antigen presentation machinery (beta-2 microglobulin, major histocompatibility complex [MHC] Class I, and MHC Class II).

Pharmacodynamic changes in the presence or abundance of immunoregulatory proteins and other proteins will be sought. Baseline and pharmacodynamic measures may also be correlated with clinical outcomes.

Laser capture microdissection may be utilized to enrich specific regions of tumor material for use in similar or additional downstream applications. This enrichment may provide robust signals of immunomodulation that are not otherwise detectable when tumor material is prepared using conventional methods. Downstream applications may include, but are not limited to, cytometry, ELISA, and/or assessment of miRNA, and gene expression. This process may be used to corroborate potentially weak signals observed by standard IHC, RNA, and/or miRNA expression experiments described above.

Tumor tissue may also be used to investigate receptor occupancy and for proteomic analysis or other exploratory analysis of protein expression and characterization.

T-cell receptor sequencing of T-cells derived from the tumor may be evaluated for association with clinical response and to understand pharmacodynamic changes.

Lastly, DNA may be extracted from a portion of tumor material to monitor somatic mutations that may impact response and other efficacy measures. Tumor mutational load has been associated with response to immunomodulatory agents, including nivolumab.[60]

9.8.3 Tissue Markers from Archived Tumor Samples

In addition to fresh tumor biopsy (see Section 9.8.2), an archival FFPE tumor tissue block (preferred) or slide (minimum of 20 slides) samples from a primary or metastatic site are to be provided by all participants, if available. Molecular characterization of archival specimens will be similar to the characterizations described above but is likely to focus on the expression of candidate markers associated with response to FRACTION-RCC study treatment combination. As described above, DNA may be extracted from a portion of the tumor material for mutational analysis. Lastly, RNA may be quantified from archival specimens using in situ hybridization, real-time PCR, or similar methodologies. Comparing protein expression, RNA expression, and mutation profiles in archival versus fresh specimens may provide insights into the molecular basis for disease progression.

9.8.4 Additional Research Collection

Additional research collections are mandatory for all participants, except where prohibited by local laws and regulations or where specific waiver is provided by the BMS Medical Monitor (or designee); if one of these exceptions occur, participation in additional research collection should be encouraged but will not be a condition of overall study participation.

This protocol will include residual sample storage for additional research. Samples to be included are peripheral blood samples for PK, immunogenicity, and biomarker analysis (including derived material), and tumor tissue.

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

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

All residual blood and tissue samples will be retained by the BMS Biorepository for additional research purposes.

Samples will be securely stored by the BMS Biorepository in Hopewell, NJ or at a BMS-approved third-party storage management facility.

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

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

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

9.8.5 Immunogenicity Assessments

Separate detailed instructions for the collection, processing, handling, labeling, storage, and shipment of PK and immunogenicity samples will be provided in the Laboratory Procedures Manual.

The details pertaining to the timing of immunogenicity sample collection for the On-treatment Phase and Follow-up are provided in each FRACTION-RCC Sub-Protocol.

The serum samples will be banked for analyses of ADAs by validated immunoassays. In addition, selected serum samples may be analyzed by an exploratory method that detects ADAs for technology exploration purposes; exploratory results will not be reported. Serum samples

designated for PK or biomarker assessments may also be used for immunogenicity analysis, if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

9.8.6 RNA Transcriptome Research

See Section 9.8.2.2.

9.8.7 RNA Expression Research of a Subset of RNA Species

Not applicable.

9.8.8 Proteome Research

See Sections 9.8.1.3 and 9.8.2.1.

9.8.9 Metabolomic Research

Not applicable.

9.8.10 Other Assessments

Not applicable.

9.9 Medical Resource Utilization and Health Economics

Not applicable.

10 STATISTICAL CONSIDERATIONS

Additional statistical considerations may be provided in each subprotocol. Please refer to the specific sub-protocol for guidance.

10.1 Sample Size Determination

Sample sizes are guided by Simon 2-stage (optimal) designs. Because of the different participant populations (anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment-naïve versus anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment-experienced) and existing care options under each Track, different criteria are applied to determine the number of participants for each stage and the strength of the efficacy signal that would recommend proceeding to the next stage. Details are described in subsequent sections and in Table 10.1-1.

For sample size calculation and for simplicity of description, recommendations for stopping or progressing to the next stage are based on the number of objective responses observed. However, since best overall response (BOR) does not necessarily capture the full extent of clinical benefit and since response can be delayed or of short duration, the BMS Medical Monitor (or designee) will also review other aspects of clinical benefit that may better predict OS benefit, such as DOR and PFSR, as well as the relative performance of different study treatment combination arms, before making a final determination.

Enrollment may continue after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response or for additional considerations that may be needed in Stage 2 such as PK/PD analyses. In such cases, the total

number of participants enrolled will not exceed the specified total number of participants treated in that arm according to Simon 2 stage. Although the sample size calculations are based on efficacy considerations, safety will also be continuously assessed and will be taken into account in the decision to continue or terminate a study treatment arm. In Track 2, 41 participants per study treatment arm in Stages 1 and 2 combined will result in 88% probability of detecting an AE that has a true rate of 5%. More participants per study treatment arm in Stages 1 and 2 combined will result in a higher probability of detecting an AE that has a true rate of 5%.

Table 10.1-1: Simon 2-Stage (Optimal) Design Consideration

Track	Historical ORR/Target ORR	Stage 1 Responders/Stage 1 n		Stage 2 Responders/Total n		Expected n with Historical ORR	Expected n with Target ORR
		Consider Futility	Go to Stage 2	Consider Futility	Consider Efficacy		
1	30% / 50%	≤ 8/24	≥ 9/24	≤ 24/63	≥ 25/63	34.5	60.0
2	5% / 20%	≤ 1/21	≥ 2/21	≤ 4/41	≥ 5/41	26.6	39.8

Note: Numbers of responses serve as a guideline; however, the totality of efficacy data will be considered when making decisions to terminate or continue an arm.

The Track 1 Simon 2-stage (optimal) design assumes a historical response rate of 30% and a target response rate of 50%, based on the observed response rate of approximately 40% for the nivolumab and ipilimumab combination in Study CA209016 and approximately 25% for nivolumab monotherapy in Study CA209025. A false positive rate of 5% and power of 90% are used.

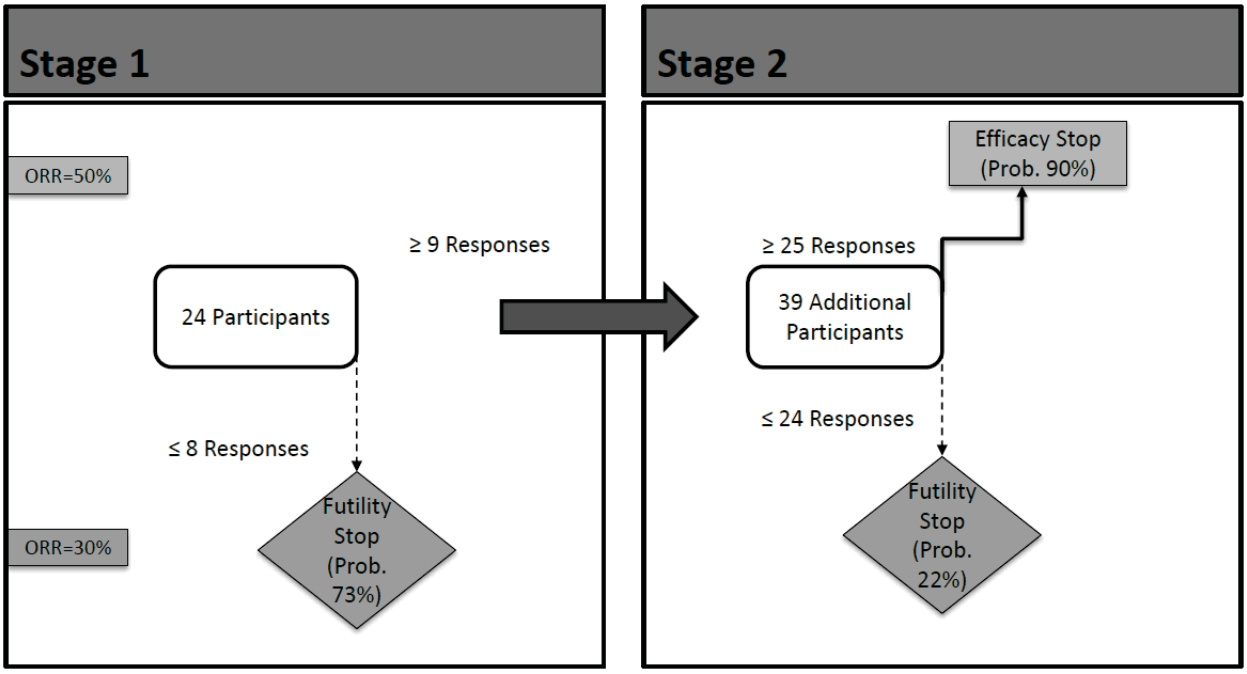
Because there is very little data available on participants with prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment, the Track 2 design is not based on an observed historical response rate. Rather, the assumption is made that a response rate below 5% would not be worth further study and that a target response rate of 20% would be worth pursuing in this population. A false positive rate of 5% and power of 90% are used. With regard to sample size, participants who are re-randomized to a different study treatment in Track 2 will be counted once for each randomization; participants who are retreated within the same study treatment arm will only be counted once.

10.1.1 Track 1 - Anti-PD-1, Anti-PD-L1, and Anti-CTLA-4 Treatment-naïve

As shown in Table 10.1-1, a minimum of 24 participants in each study treatment combination arm will be treated in Stage 1 for an initial evaluation of efficacy. If the number of responses observed in Stage 1 is $\leq 8/24$, the study treatment combination arm would likely not be considered efficacious; otherwise, enrollment to Stage 2 will continue, and an additional 39 participants will be treated. If the total number of responses at the end of Stage 2 is $\leq 24/63$, the study treatment arm will be terminated for futility; if there are more than 24 responses observed at the end of Stage 2, the study treatment combination may be carried on for further treatment development. The totality of efficacy data and response profile for each combination will be considered when making decisions to terminate or continue an arm.

The operating characteristics of this Simon 2-stage (optimal) design are provided in Figure 10.1.1-1. With the stopping boundaries as shown in Table 10.1-1, if the combination has an ORR no better than the historical control at 30%, then there is a 95% overall chance of stopping for futility, with a 73% chance of stopping at Stage 1; there is a 5% false positive rate. If the combination has an ORR equal to the target of 50%, then there is a 90% chance of stopping for efficacy after Stage 2, whereas if the true ORR is 35%, 40%, or 45%, the power would be 20%, 48%, or 74%, respectively.

Figure 10.1.1-1: Operating Characteristics of Track 1 Simon 2-stage (Optimal) Design (Power =90%, Alpha = 5%)



Abbreviation: ORR = overall response rate; prob = probability.

If 25 responses are observed at the end of Stage 2 (Efficacy Stop), then the 90% CI for ORR will be [29%, 51%]. The CI is calculated using the Clopper-Pearson method.

As stated in Section 10.1, the number of responses given here is used for sample size calculation and for simplicity of description. Before making a decision to terminate or continue an arm, BMS will also review the totality of all available data, which includes: other aspects of efficacy that may help predict OS benefit, such as DOR and PFSR; clinical safety information; and biomarker data; as well as the relative performance of other treatment arms.

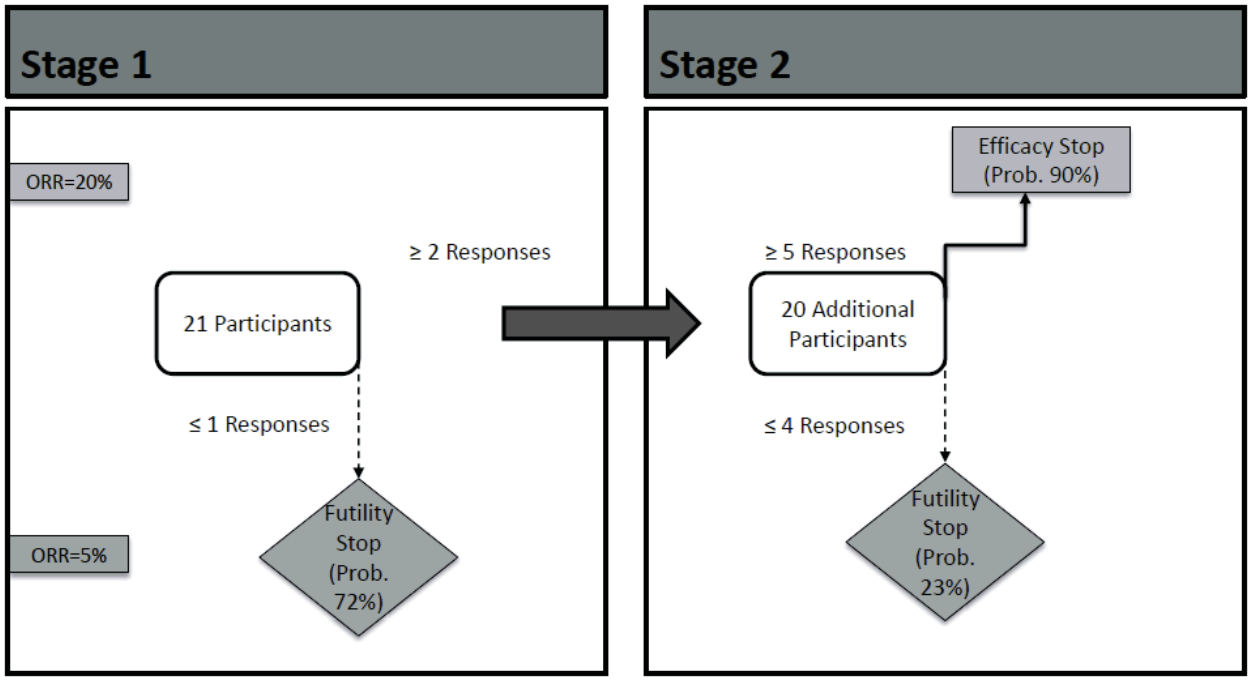
10.1.2 Track 2 - Anti-PD-1, Anti-PD-L1, or Anti-CTLA-4 Treatment-experienced Participants

For each study treatment combination arm under Track 2, the Simon 2-stage (optimal) design will be used. Initially, 21 participants per study treatment combination arm will be treated in Stage 1, and preliminary efficacy will be assessed when those participants are evaluable. If 1 or fewer responses are observed in Stage 1, the study treatment arm would likely not be considered efficacious; otherwise, Stage 2 will be initiated and enroll an additional 20 participants, for a total of 41 participants per study treatment combination arm. The totality of efficacy data and response profile for each combination will be considered when making decisions to terminate or continue an arm.

The operating characteristics of this Simon 2-stage (optimal) design are provided in Figure 10.1.2-1. With the stopping boundaries as shown in Table 10.1-1, if the combination has an ORR no better

than 5%, then there is a 95% overall chance of stopping for futility, with a 72% chance of stopping at Stage 1; there is a 5% false positive rate. If the combination has an ORR equal to the target of 20%, then it has a 90% chance of stopping for efficacy after Stage 2.

Figure 10.1.2-1: Operating Characteristics of Track 2 Simon 2-stage (Optimal) Design (Power =90%, Alpha = 5%)



Abbreviation: prob = probability.

If 5 responses are observed at the end of Stage 2 (Efficacy Stop), then the 90% CI for ORR will be [5%, 24%]. The CI is calculated using the Clopper-Pearson method.

As stated in Section 10.1, the number of responses given here is used for sample size calculation and for simplicity of description. Before making a decision to terminate or continue an arm, BMS will also review the totality of all available data, which includes: other aspects of efficacy that may help predict OS benefit, such as DOR and PFSR; clinical safety information; and biomarker data; as well as the relative performance of other treatment arms.

Both participants previously treated in any Track (re-randomized participants) and new participants who meet eligibility criteria are permitted to enter Track 2. Some slots in Track 2 will be reserved for re-randomized participants to ensure that both types of participants are enrolled in Track 2. At the initiation of the study, recruitment of re-randomized participants will be limited to 11 participants per Track 2 study treatment combination arm in Stage 1 (with 25% dropout rate considered). In Stage 2, recruitment of additional re-randomized participants will be limited to 12 participants out of the 27 additional participants (with 25% dropout rate considered). The limited number of re-randomized participants may be re-adjusted depending on the enrollment

rates, the rate of progression in Tracks 1 and 2, and the number of currently open study treatment arms in Track 2.

10.1.3 Tracks 1 and 2 Pharmacodynamic/Biomarker Assessment

To assess the pharmacodynamic effects of FRACTION-RCC combination or nivolumab in combination with ipilimumab as stated in the exploratory objective, pretreatment and On-treatment whole blood, serum samples, and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of On-treatment biomarker assessments to pretreatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable with log-normal distribution, a given number of participants per study treatment arm under different Track will provide the confidence that the estimate of the ratio of On-treatment to baseline values will be within 20% of the true value, as shown in Table 10.1.3-1.

Table 10.1.3-1: Probability That Estimated Ratio of On-treatment to Pretreatment (Baseline) Value Is Within 20% of True Value

Intra-participant Standard Deviation (Log-scale)		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	N = 21	100%	97%	89%	81%	72%	65%	59%
	N = 24	100%	98%	92%	84%	75%	68%	62%
	N = 41	100%	100%	97%	93%	87%	81%	75%
	N = 63	100%	100%	99%	97%	94%	89%	84%

Abbreviations: N = number of participants.

For example, for a biomarker (eg, activated and memory CD4 and CD8 T-cells) with an intra-participant standard deviation of 0.5, if the true ratio of postbaseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 93% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 41 participants per study treatment arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 93% probability that the estimated percent change would be between 28% and 92% with 41 participants per study treatment arm.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 10.2-1: Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All participants who are randomized to any study treatment arm of any Track in this study.
Treated	All participants who are randomized and take at least 1 dose of study treatment

Table 10.2-1: Populations for Analyses

Population	Description
PK	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have available immunogenicity assessment data
Biomarker	All treated participants who have available biomarker data
Response-evaluable	All treated participants with measurable disease and one of the following: 1) at least 1 postbaseline tumor measurement, 2) clinical progression, or 3) death.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

The primary efficacy analyses will be performed on the treated population for the final analysis. Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Details on censoring scheme on time-to-event endpoints such as DOR, progression-free survival (PFS), and OS will be described in the statistical analysis plan.

Table 10.3.1-1: Efficacy Analyses

Endpoint	Statistical Analysis Methods
ORR BOR for a participant will be assessed per RECIST v1.1 by investigator.	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by study treatment under each Track.
Median DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Median DOR using the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by study treatment under each Track.
PFSR at 24 weeks PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula by study treatment under each Track.
OS rate at certain time points OS for a participant is defined as the time from the first dosing date to the date of death due to any cause.	Estimate by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula by study treatment under each Track.

Treatments under each Track for different populations will be analyzed independently. There is no intention to combine the same study treatment across Tracks for efficacy analyses.

Participants re-randomized into Track 2 will be combined with participants originally randomized into Track 2 for efficacy analysis.

Specific analyses to be performed for each Track are shown in Table 10.3.1-2.

Table 10.3.1-2: Analyses Planned for Each Track

Track		ORR	DOR	PFSR	OS
Track 1	End of Simon Stages 1 and 2	X	X	X	X
Track 2	End of Simon Stages 1 and 2	X	X	X	X
	Early Termination at Simon Stage 1			X	X

Abbreviations: DOR = duration of response; ORR = overall response rate; OS = overall survival; PFSR = progression free survival rate.

Track 1 - Anti-PD-1, Anti-PD-L1, and Anti-CTLA-4 Treatment-naïve Participants

The following additional analyses will be performed for Track 1 anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment-naïve participants at the end of Stage 2. These efficacy analyses will be performed when the study treatment arms have been fully enrolled and followed up for at least 6 months. A descriptive odds ratio and estimate of the difference in ORRs, along with corresponding 2-sided 95% CIs, will be provided to evaluate differences between the 2 randomized study treatment arms (FRACTION- RCC study treatment combination arm and nivolumab in combination with ipilimumab control arm). Additionally, for each study treatment arm, the ORR and corresponding 95% CIs will be calculated using Clopper-Pearson method. A descriptive hazard ratio and corresponding 2-sided 95% CI of PFS and OS will be estimated in a Cox proportional hazards model using study treatment as a single covariate to evaluate difference between the 2 study treatment arms (experimental and control arms). The PFS and OS curves for each study treatment arm will be estimated. Two-sided 95% CIs for median PFS and OS will be computed. PFSR at 24 weeks and survival rates at certain time points (eg, 2 years) will be estimated. Associated 2-sided 95% CIs will be calculated.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Table 10.3.2-1: Safety Analyses

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs leading to discontinuation and deaths. AEs will be graded according to CTCAE Version 4.03.	Frequency distribution of treated participants with AE using the worst CTC grade on treatment. Participants will be counted once at the PT level, once at the system organ class level, and once in the "Total subject" row at their worst CTC grade, regardless of SOC or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE Version 4.03.	Laboratory shift table using the worst CTC grade on treatment per participant.

Abbreviations: AE = adverse event; CTC = common terminology criteria; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

Same treatments under different Tracks with different populations may be combined for safety analyses.

10.3.3 Other Analyses

Not applicable.

10.3.3.1 Pharmacokinetic Analyses

The concentration-time data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of each component of each FRACTION-RCC study treatment combination and/or nivolumab in combination with ipilimumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model-determined exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. Results of population PK and exposure-response analyses will be reported separately.

10.3.3.2 Immunogenicity Analyses

Table 10.3.3.2-1: Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to individual component of study treatment combination Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline.[a] An ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the study treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the study treatment

[a] Baseline sample is the last sample before initiation of the study treatment
Abbreviations: ADA = anti-drug antibody.

10.3.3.3 Exploratory Biomarker Analyses

Table 10.3.3.3-1: Exploratory Biomarker Analyses

Endpoint	Statistical Analysis Methods
Summary measures of change (or % change) from baseline in various biomarkers in the tumor and peripheral blood	Summary statistics by planned study day and treatment under each Track; plots of the time course of biomarkers

If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic regression will be used to explore possible associations between biomarker measures from peripheral blood or tumor biopsy and clinical outcomes. Additional details will be provided in the statistical analysis plan. Exploratory biomarker/pharmacodynamic analysis may be presented separately from the main clinical study report.

10.3.3.4 Outcomes Research Analyses

Table 10.3.3.4-1: Outcomes Research Analyses

Endpoint	Statistical Analysis Methods
Summary measures of EQ-5D-3L index and VAS scores and FKSI-DRS score with corresponding change from baseline for each score EQ-5D-3L index scores will be derived using the United Kingdom weighting algorithm	Summary statistics by planned study day and treatment under each Track
Questionnaire completion rate Defined as the proportion of questionnaires actually received out of the expected number	Summary statistics by planned study day and treatment under each Track
Proportion of participants reporting no, moderate, or severe problems in each of the 5 EQ-5D-3L dimensions Proportion will be based on the number of participants assessed at each assessment time point	Summary statistics by planned study day and treatment under each Track

Abbreviations: EQ-5D-3L = 3-level version of EQ-5D self-report questionnaire; FKSI-DRS = Functional Assessment of Cancer Therapy-Kidney Symptom Index-disease-related symptoms; VAS = visual analog scale.

10.3.4 Interim Analyses

Data from individual study treatment arms under each Track of this study may emerge at different times; timely decisions (including early termination) for each individual study treatment under different Tracks are needed. Database lock and analysis for certain FRACTION-RCC study treatment combination arms will be performed when all participants in these study treatment combination arms (under each Track) have completed treatment and with sufficient follow-up. Potential interim analyses for each study treatment combination arm under each Track at the end

of Stage 1 (6 months after first treatment date of the last participant within that study treatment arm) will be performed. These interim analyses will be performed independent of each other.

The SMB will have access to interim reports of safety and will provide advice to the Sponsor regarding study treatment arm termination due to safety concerns.

The statistical analysis plan will further describe the planned interim analyses.

Additional interim analyses may also be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BATTLE	Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BUN	blood urea nitrogen
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
DNA	Deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EOT	end of treatment
EQ-5D-3L	3-level version of EQ-5D self-report questionnaire
EU	European Union
FFPE	formalin fixed, paraffin embedded

Term	Definition
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index disease-related symptoms
FRACTION	Fast Real-time Assessment of Combination Therapy in Immuno-ONcology
FSH	follicle stimulating hormone
FU	follow-up
GI	gastrointestinal
GITR	glucocorticoid-induced tumor necrosis factor receptor-related (gene)
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIFα	hypoxia-inducible factor alpha
HIV	human immunodeficiency virus
IB	Investigator's Brochures
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IHC	immunohistochemical/immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IMP	investigational medicinal product
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
I SPY 1/2 TRIAL	Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis
KPS	Karnofsky Performance Status
[redacted]	[redacted]
LDH	lactate dehydrogenase
MHC	major histocompatibility complex
miRNA	micro ribonucleic acid
mRCC	metastatic renal cell carcinoma

Term	Definition
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mechanistic target of rapamycin
N1 + I3	nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg
N3 + I1	nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg
NCI	National Cancer Institute
NCI-MATCH	NCI Molecular Analyses for Therapy Choice
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
p-DILI	potential drug-induced liver injury
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PFSR	progression-free survival rate
PID	patient identification number
PK	pharmacokinetic
PR	partial response
prob	probability
PT	preferred term
QTcF	QT interval corrected with Fridericia's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical analysis plan

Term	Definition
SD	stable disease
SMB	Safety Monitoring Board
SOC	system organ class
SUSAR	suspected, unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAPUR	Targeted Agent and Profiling Utilization Registry
TKI	tyrosine kinase inhibitor
TNFRsf	tumor necrosis factor receptor super family
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VEGF	vascular endothelial growth factor
WOCBP	women of child-bearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'subject' used in the electronic case report form (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 the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A 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, 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 (eg, loss of medical licensure or debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

If a deviation or a 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 the IRB/IEC or 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(ies) 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.

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant to inquire about the details of the study.

- Obtain an informed consent signed and personally dated by the participant 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.

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 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 participants' signed informed consent form, and, in the United States, the participants' signed Health Insurance Portability and Accountability Act (HIPAA) authorization.

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

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

For the Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) Program, participants should receive consent forms that include relevant information for all treatments to which they are eligible for enrollment; participants will not receive consent forms that include data relevant to agents within the FRACTION Program that are not within the Sub-Protocol for which they are screened. Informed consents to Sub-Protocols that are closed, terminated early, or in any way no longer in effect will not be provided to new participants as an eligible treatment consent. Participants in any follow-up phase for a Sub-Protocol that is closed or terminated will receive pertinent updated safety and risk information if it becomes known. Participants in any follow-up phase may receive revised informed consent via mail and follow-up phone call by the investigator site.

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 (eg, lost or 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	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the standard operating procedures (SOPs)/standards of the sourcing pharmacy.

If	Then
vendors (examples include IP sourced from the sites' stock or commercial supply, or a specialty 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.

Abbreviations: IP = investigational product; SOP = standard operating procedure.

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 case report form (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 adverse events (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, eCRFs will be prepared for all data collection fields, except for fields specific to serious adverse events (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, including SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician, who is a subinvestigator and who was delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For eCRFs, 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 eCRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

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

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

RECORDS RETENTION

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

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

If the investigator withdraws from the study (eg, relocation or retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, or 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 or 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 treatment containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS or its vendors (examples include study treatments sourced from the sites' stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

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 (eg, 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 treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point where the Investigational Medicinal Product (IMP) or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of

safety margins from the no-observed adverse effect level or the time required for 5 half-lives of the IMP to pass.

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 approximately 5 half-lives after the end of study treatment, plus 30 days

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – 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 and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited) [b,c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected.

• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine 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

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS 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 will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should

continue to use a condom while on study plus 5 half-lives of study treatments plus 90 days (duration of sperm turnover). Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined 5 half-lives plus an additional 90 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, while on study plus 5 half-lives of study treatments plus 90 days (duration of sperm turnover). Withdrawal (coitus interruptus) and/or the use of a spermicide without a condom are not acceptable methods of contraception or fetal protection.
- Refrain from donating sperm for the duration of the study treatment and 5 half-lives plus an additional 90 days 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 RECIST v1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.1 Measurable lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 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). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

1.4.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical lesions

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 by both 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.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target lesions

When more than one measurable lesion is present at baseline all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

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 below, 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.

2.1.1 Lymph nodes

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. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

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 and should be 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.

3.1.1.2 Target lesions that become 'too small to measure'

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). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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: in case of a lymph node believed to be present and 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).

3.1.1.3 Target 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.
- 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

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* 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 non-target lesions

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

3.2.1.1 When the subject also has measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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 subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. 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 subject'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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject'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.*

3.3.1 FDG-PET evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment 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:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 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 positive 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.

4 RESPONSE CRITERIA

4.1 Timepoint response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Table 1. Time point response: subjects 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, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation scans

- **Verification of Response**: Confirmation of PR and CR is required at least 4 weeks later to ensure responses identified are not the result of measurement error. 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**: Not required.

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the objectively documented progression per RECIST v1.1 or subsequent anticancer therapy, whichever occurs first (taking into

account any requirement for confirmation). The subject'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.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 weeks).

Table 2. Best overall response when confirmation of CR and PR *IS* required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[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 subject 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.

4.3 Duration of response

4.3.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 6 NIVOLUMAB MANAGEMENT ALGORITHMS

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

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

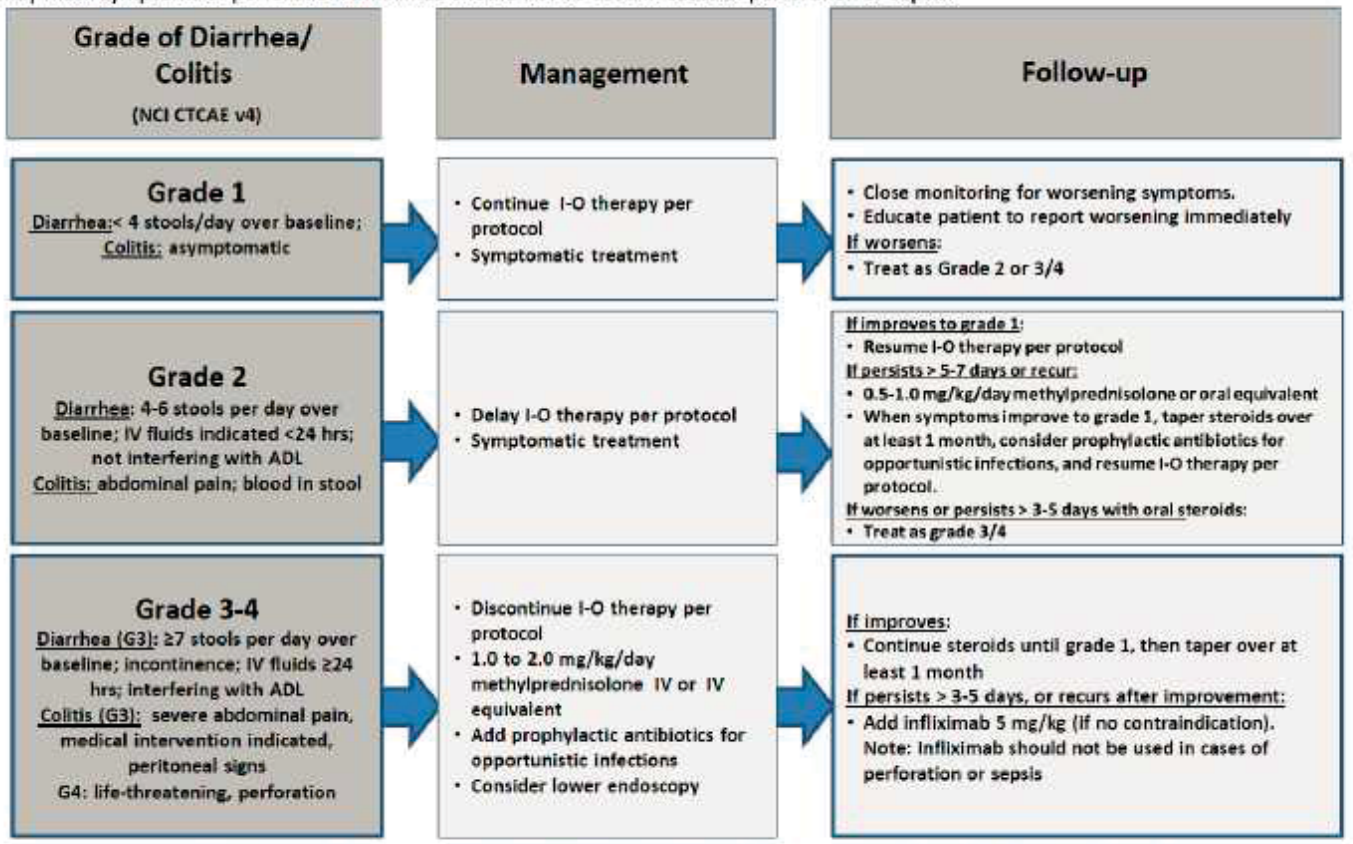
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

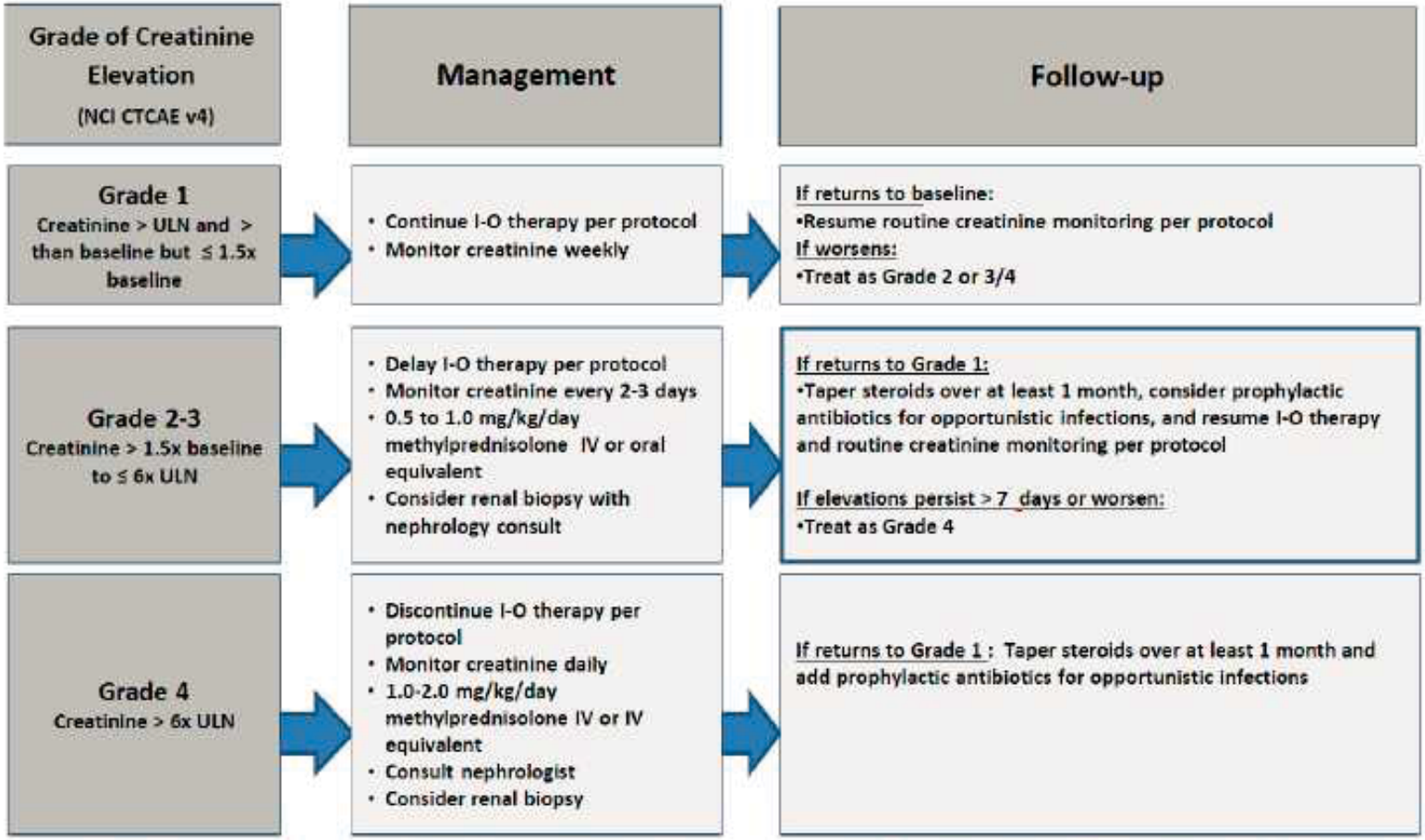


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Renal Adverse Event Management Algorithm

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

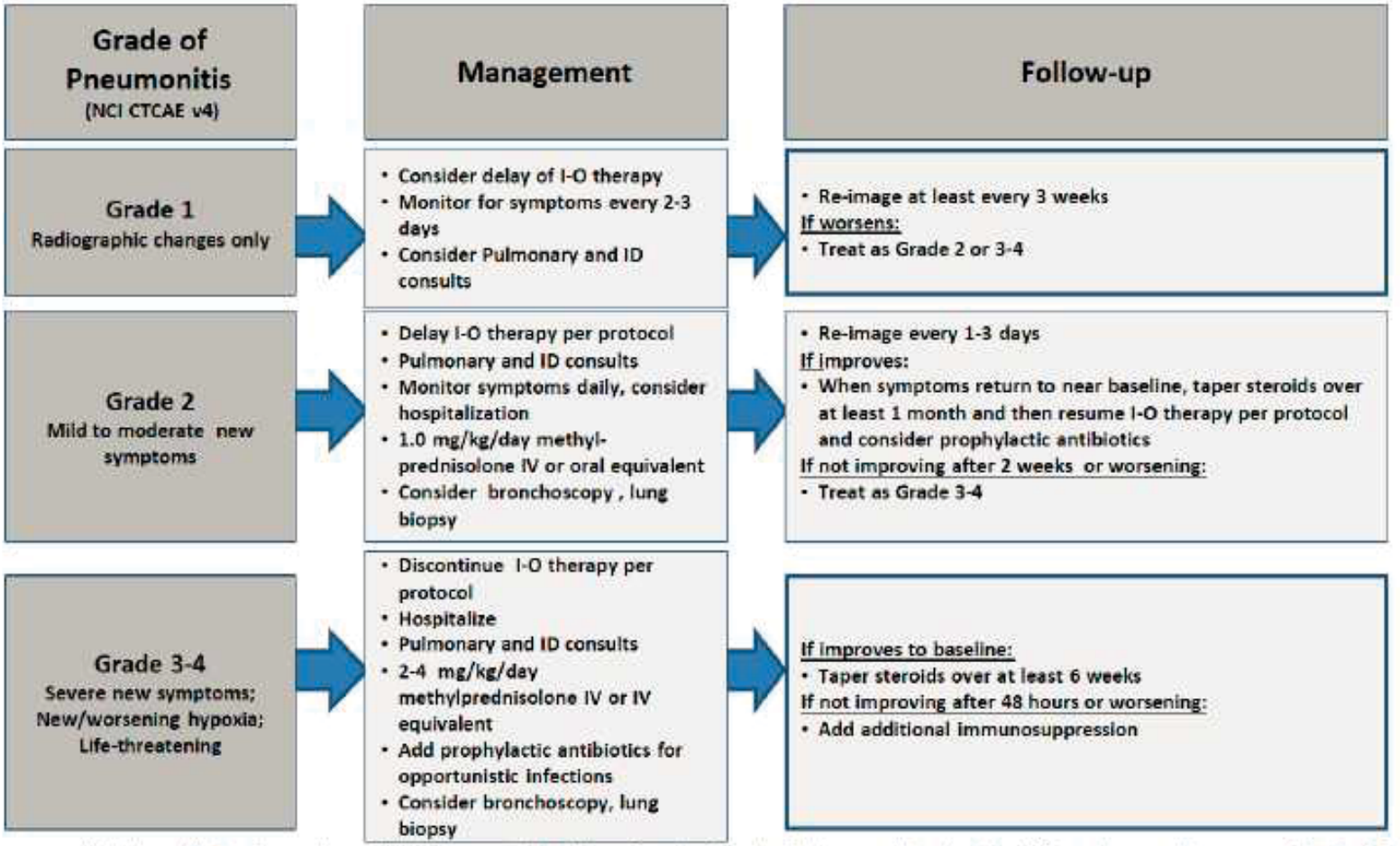


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Pulmonary Adverse Event Management Algorithm

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

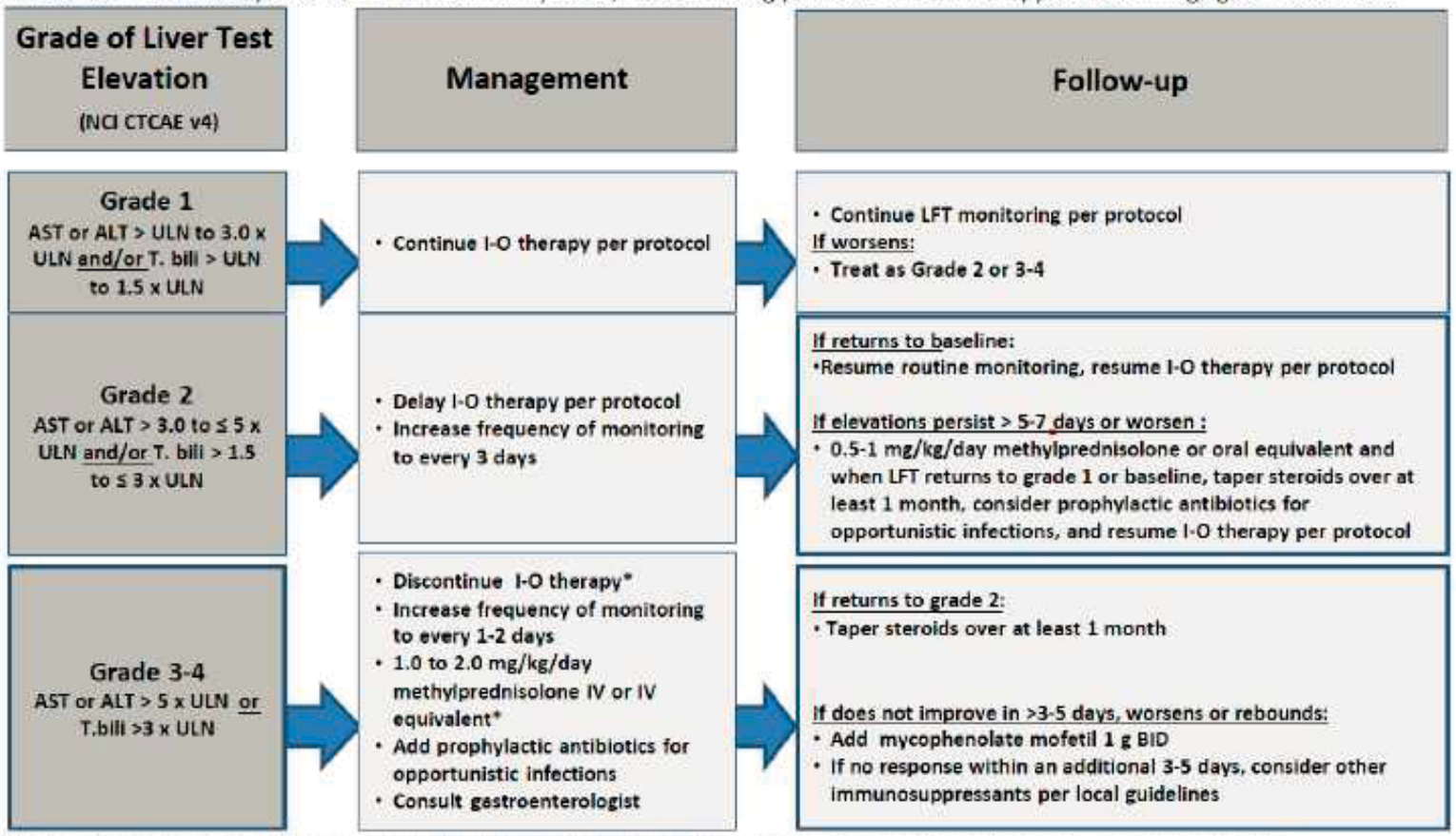


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Hepatic Adverse Event Management Algorithm

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



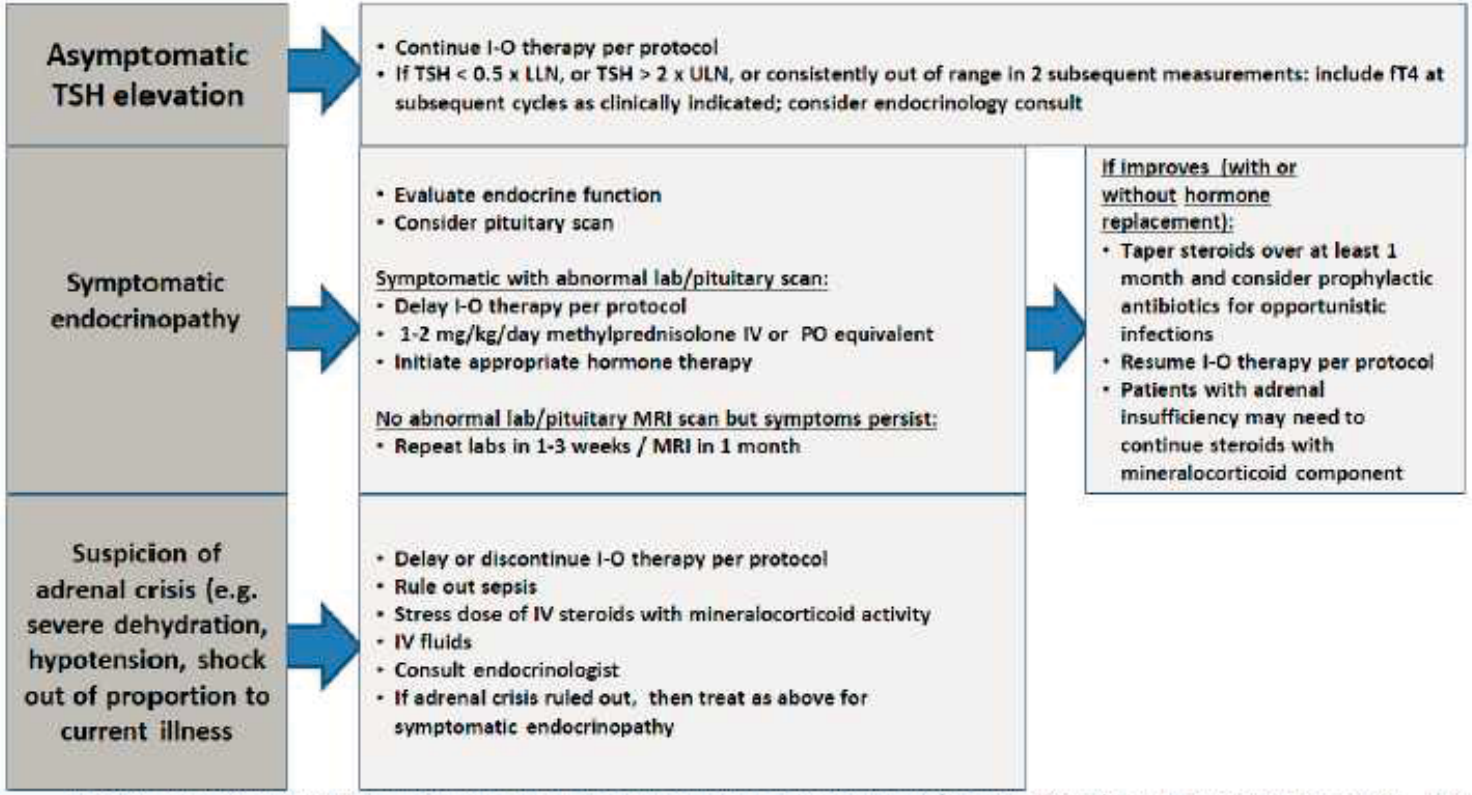
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

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

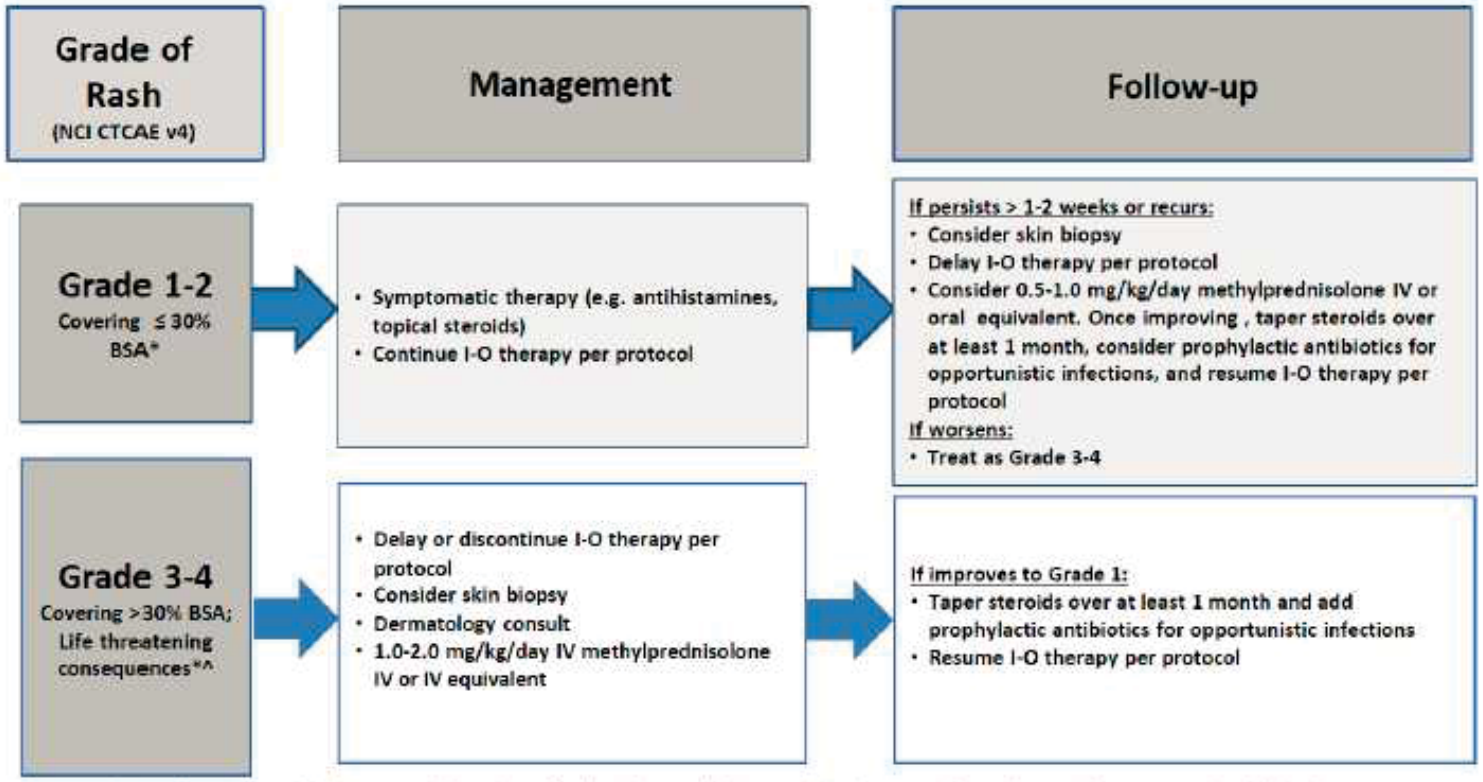


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Skin Adverse Event Management Algorithm

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



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

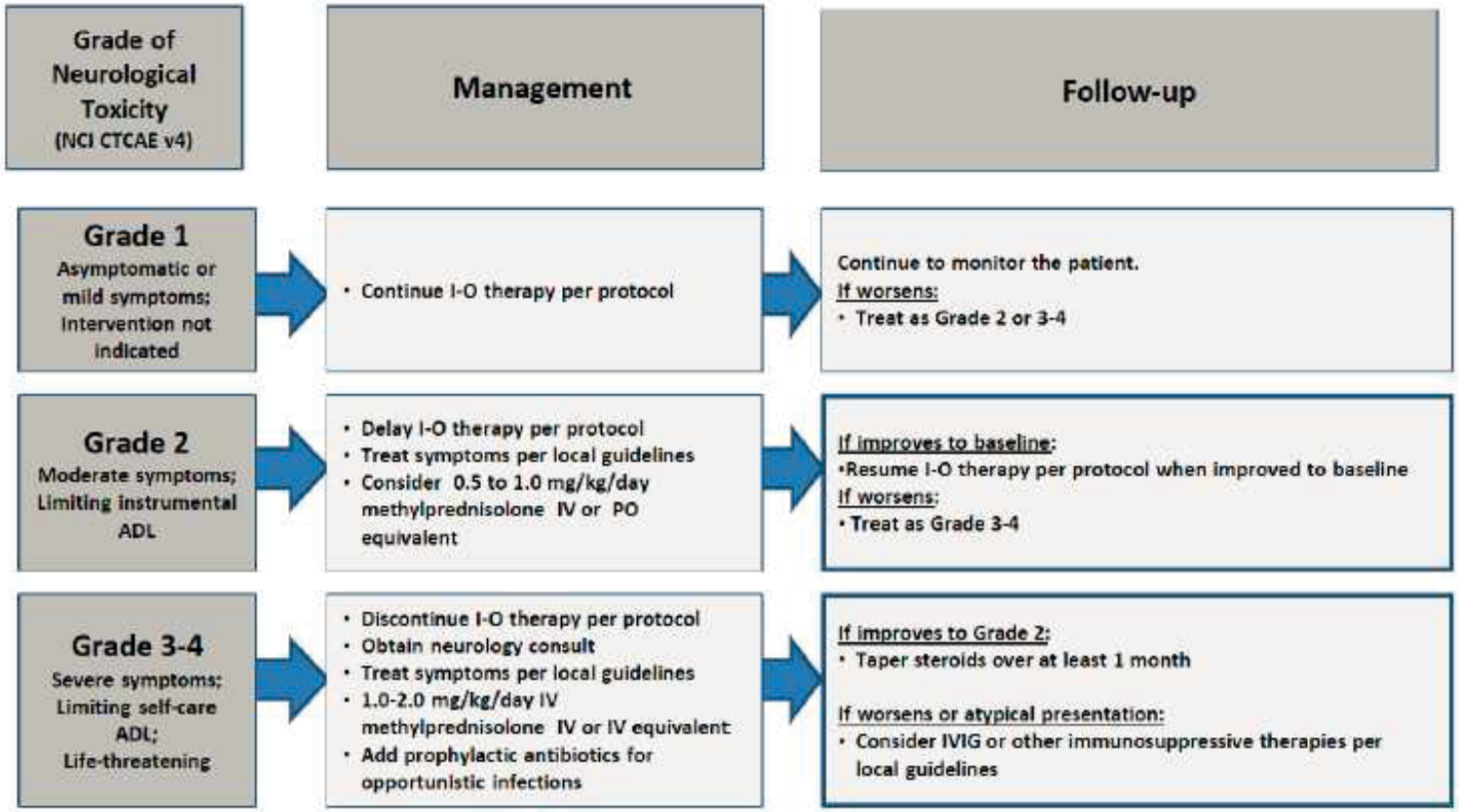
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

27-Jun-2018

Neurological Adverse Event Management Algorithm

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



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

27-Jun-2018

APPENDIX 7 KARNOFSKY PERFORMANCE STATUS

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

APPENDIX 8 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

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

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

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

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

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

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

APPENDIX 9 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 06, 15-Nov-2018

Section 2 Schedule of Activities, Table 2-1 Screening Procedural Outline in FRACTION-RCC Cancer Revised Protocol was modified to include clarification of ECG procedure. Section 4 Objectives and Endpoints was modified to update Tertiary/Exploratory Objective 6 per planned analysis of patient-reported outcomes data. Section 6.1 Inclusion Criteria were modified to clarify favorable risk profile and Karnofsky Performance Status requirements. Section 9.1 Efficacy Assessments was edited to provide language consistent with Table 2-1 and clarify collection of details of progressive disease in relation to participant's prior therapy. Section 7.7.1 Prohibited and/or Restricted Treatments was modified to include language clarifying marijuana use. Paragraphs describing activities related to patient-reported outcomes were moved to Section 9.1.2 Patient-reported Outcomes. Other key changes include updates made to safety guidance and/or reporting activities to align the protocol with current policies and safety parameters, in the following sections: Section 9.2.5 Pregnancy; Section 9.3 Overdose; Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting; Appendix 4, Contraception Guidance for Female Participants of Child Bearing Potential; and Appendix 6 Hepatic Adverse Event Management Algorithm.

Summary of key changes of Revised Protocol 06

Section Number & Title	Description of Change	Brief Rationale
Section 2, Schedule of Activities; Table 2-1: Screening Procedural Outline; Table 2-2: Baseline for Re-randomization Procedural Outline Table 2-3: Follow-Up Procedural Outline	Notes for Utilize IRT were modified and time to randomization is now 5 - 7 days. Modified to read: ECGs should be recorded after the participant has been supine for at least 5 minutes. Record QTcF. If ECG abnormality is noted, a repeat ECG must be performed. Clarified the collection windows for scans during the follow up period. Clarified that patient-reported outcomes can be collected over the phone if needed.	Compliance with current IRT manual. The changes were made based on recent need for assessment of ECG in sub-protocol C. Clarified the collection windows for tumor response assessment. Allows patient-reported outcomes information to be collected even if visit is delayed.
Section 4, Table 4-1 Objectives and Endpoints	Modified Tertiary/Exploratory Objective 6 to read "To evaluate changes in disease-related symptoms, as measured by the FKSI-DRS, in treated participants".	Changed since the patient-reported outcomes data are to be analyzed using descriptive statistics and because no directional hypothesis is specified for EQ-5D outcomes.
Section 6.1 Inclusion Criteria	Modified to read: 2)e)i)6) Based on the results from CheckMate-214 participants with favorable risk profile by IMDC Score must have been treated with sunitinib prior to randomization into Track 1 nivolumab plus ipilimumab". Added:	The word, "favorable" and KPS was inadvertently missed during protocol version 05. This was a typographical error. KPS status requirements were specified.

Summary of key changes of Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	2)e)i)7) Karnofsky Performance Status (KPS) must be ≥ 70% (Appendix 7) 3)f) Added text to address fetal protection.	Required by [redacted] (Women Of Child Bearing Potential and Clinical Trials Policy)
Section 7.7.1 Prohibited and/or Restricted Treatments	Added that use of marijuana and its derivatives are permitted for treatment of symptoms related to cancer treatment to 4th bullet.	Marijuana has become legalized in many geographic regions and is increasingly being used for cancer patients. Multiple institutions have requested the use of marijuana in the protocol as patients are legally utilizing marijuana for multiple purposes, including but not limited to pain, poor/loss of appetite, anxiety, anorexia, and nausea.
9.1 Efficacy assessments	Added: All participants should receive scans at FU1, except for participants with PD who started subsequent therapy or have already been treated beyond progression. Scans at FU3 and every 12 weeks will only be collected for patients with CR, PR, or SD at treatment discontinuation. Added: As participant's response to prior therapy is an important part of medical history, additional details regarding the previous therapy, including but not limited to best response to therapy, timing of progression on prior therapy, method of how the progression was measured, existence of confirmation scan to document progression and detailed information such as other clinical evidence (e.g. increased pain requiring palliative radiotherapy) to support progression, response/progression dates, and reason for discontinuation will be collected in this trial.	Clarification language to be consistent with tumor assessments for f/u periods in Schedule of Assessments (SOA) Addition of collection of details of progressive disease in relation to participant's prior therapy.
9.1.2 Patient-reported Outcomes	Moved paragraphs describing activities related to patient reported outcomes from Section 9.9.1 to Section 9.1.2.	Patient-reported outcomes reflect efficacy, rather than medical resource utilization and health economics in this study.
9.2.5 Pregnancy	Text added to address fetal protection.	Required by [redacted] (Women Of Child Bearing Potential and Clinical Trials Policy)

Summary of key changes of Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.3 Overdose	Modified the section to state that "All events meeting the definition of overdose must be reported as an AE/SAE" and added a reference to Appendix 3.	Modified text to be consistent with revised language in Appendix 3.
Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Updated the safety reporting appendix to include current language on AEs and SAEs related to progressive disease and overdose.	Clarified the need to report abnormal lab tests or other safety assessments when the final diagnosis is not available. Included language to clarify that disease-related events and events associated with lack of efficacy will be reported as AEs if the event meets the criteria of an AE. Text was added to clarify the need for the investigator to report the specific term of "intentional overdose" as an AE term. All other types of overdose should NOT be reported as an AE but should be recorded elsewhere on the CRF. There are no changes to the reporting of AEs associated with any type of overdose.
Appendix 4, Contraception Guidance for Female Participants of Child Bearing Potential	Changes to instructional text and prompt choice 2 (Male Partners WOCBP - Choice: Teratogenic/Non-Genotoxic)	Required by [redacted] (Women Of Child Bearing Potential and Clinical Trials Policy)
Appendix 6 Hepatic Adverse Event Management Algorithm	Footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T. bili ≤ 5 x ULN was removed.	Language was modified to align protocol with current Nivolumab Investigator Brochure and nivolumab program safety parameters.

Overall Rationale for the Revised Protocol 05, 27-Apr-2018

Exclusion criteria in FRACTION-RCC Cancer Revised Protocol were added to exclude favorable risk patients who have not have been treated with sunitinib prior to randomization into Track 1 for treatment with nivolumab plus ipilimumab. The Schedule of Activities Table was revised to include collection of risk information as defined by International Metastatic RCC Database Consortium (IMDC) score (detailed language provided in Appendix 8), as well as testing for Methemoglobin level and Glucose-6-phosphate Dehydrogenase Deficiency. Circulating tumor DNA to Biomarker Assessment. Statistical considerations includes an updated description for enrollment of the participants. The trial design and sample size determination were modified to allow for enrollment to continue until efficacy evaluation is complete.

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1, Synopsis	Synopsis was revised to reflect the changes in the protocol body and is now included under section 1 in revised protocol 05.	Synopsis is now being added as section 1 in the revised protocol instead of stand-alone supplemental document.
Section 2, Schedule of Activities; Table 2-1: On-treatment Procedural Outline, Table 2-2, Baseline for Re-randomization Procedural Outline	Edits to tables for risk score collection, as well as methemoglobin level and Glucose-6-phosphate Dehydrogenase Deficiency testing.	Risk score collection was added based on the results of the CheckMate-214 clinical trial
Section 3.1.1.3 , Rationale for Biomarker Assessments 1) Blood-based biomarkers 2) Tumor tissue-based biomarkers	1)c) modified to read: T-cell receptor sequencing will be performed to detect expansion of antigen-directed T-cells clones, which may provide evidence of adaptive immune responses against tumor and pharmacodynamics information potentially used for combination strategy.	Plasma ctDNA for Tumor Mutational Burden Assessment was added to the list of blood-based biomarkers. Other changes describe details and rationale for the following biomarkers assessment: T-cell receptor sequencing, plasma ctDNA, whole exome or genome sequencing, gene expression analysis.
	1)e) added: Plasma ctDNA for Tumor Mutational Burden Assessment. High tumor mutational burden (TMB) is an indication for increased neo-antigen presentation in tumors, which leads to recruitment of immune cells to the tumor site and induction of anti-tumor immunity. Consequently, high TMB has been correlated with increased response to nivolumab and other therapeutics targeting the PD (L)1 axis in NSCLC. TMB can be inferred from ctDNA isolated from plasma samples. TMB results from the periphery will be compared with TMB results from whole exome sequencing of tumor tissue biopsies if sufficient slides are available. Quantitative and qualitative assessment of ctDNA can also provide insight into dominant tumor clones and their hierarchy, clonal evolution during treatment, and relevance for response and nonresponse. Plasma samples for ctDNA extraction will be collected at the indicated time points and kept frozen at -80 °C in storage. Additional use of these samples may include analysis of	

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	microsatellite instability or other clinically relevant biomarkers.	
	2)b) modified to read: Whole exome or whole genome sequencing: DNA may be extracted from biopsy specimens to monitor somatic mutations that may impact response and other efficacy measures. Whole exome, whole genome, or targeted sequencing methodologies may be employed. Tumor mutational load has been associated with response to immunomodulatory agents, including nivolumab.	
	2)c) modified to read: Gene expression analysis: RNA-seq, and/or similar methodologies, will be used to assess gene expression patterns associated with each of the expansion tumor types and to identify changes in those gene expression patterns following treatments with. Ultimately, this approach may lead to the identification of unique baseline or on-treatment RNA expression signatures that could be useful for identifying patients who are likely (or unlikely) to respond to the combination therapy. Focus may be given to monitoring a battery of immunoregulatory genes associated with cancer cells or cancer-interacting lymphocytes. Examples within the latter group include genes associated with T-cells, NK cells, and/or IFN-γ signaling. Such genes have been implicated previously in tumor responses or rejection.	
Section 5.1 Overall Design	Added rationale for continuous enrollment within section 5.1: Enrollment may continue after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response or for additional considerations that may be needed in Stage 2 such as PK/PD analyses. In such cases, the total number of subjects enrolled will not exceed the specified total number of	Added to allow enrollment to continue until efficacy evaluation complete.

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	participants treated in that arm according to Simon 2 stage.	
Section 6.1 Inclusion Criteria	Inclusion Criteria were updated to add additional criteria based on the results of CheckMate-214 clinical trial: 2)i)(5) Participants must be evaluated for risk of the disease as defined by International Metastatic RCC Database Consortium (IMDC) score (Appendix 8). 2)i)(6) Based on the results from CheckMate-214 , participants must have been treated with sunitinib prior to randomization into Track 1 nivolumab plus ipilimumab. Added clarification to criterion 3) Age and Reproductive Status: In addition to the reproductive guidelines noted below, please refer to the individual sub-protocol for additional requirements regarding reproductive guidelines.	The changes were made based on the results of the CheckMate-214 clinical trial.
Section 9.8.1.4 Circulating Tumor DNA Analysis (Plasma Biomarkers)	9.8.1.4 Circulating Tumor DNA Analysis (Plasma Biomarkers) The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In patients with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 bp and specific genomic regions can be amplified with PCR. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma from patients with known driver mutations, BEAMing technology will be utilized to count the frequency of mutations in circulation.	Added to provide rationale for ctDNA assessment.
Section 10, Statistical Considerations	Added clarification under Section 10, Statistical Considerations Additional statistical considerations may be provided in each subprotocol. Please refer to the specific sub-protocol for guidance.	Clarified where additional statistics are located

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1, Sample size determination	The following language "Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response. For example, assuming a 25% dropout rate, up to 32 additional participants per study treatment arm could be enrolled into Track 1 Stage 1 to achieve 24 "evaluable" participants (with any over-enrollment counting toward Stage 2), while in Stage 2, an additional 13 participants over the planned 39 could be enrolled to achieve 63 total evaluable participants. Similarly in Track 2 Stage 1, up to 28 participants may initially be enrolled to achieve 21 evaluable participants", is replaced with: "Enrollment may continue after reaching the indicated number of participants at Stage 1 while the initial efficacy evaluation is ongoing. Additional participants may be enrolled to account for participants who may drop out of the study without being evaluable for response or for additional considerations that may be needed in Stage 2 such as PK/PD analyses. In such cases, the total number of subjects enrolled will not exceed the specified total number of participants treated in that arm according to Simon 2 stage."	Added to allow enrollment to continue until efficacy evaluation complete.
Appendix 8	Addition of. International Metastatic RCC Database Consortium (IMDC) score	Appendix 8 was amended to provide description of International Metastatic RCC Database Consortium (IMDC) score
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 04, 08-Feb-2018

The FRACTION-RCC Master protocol was revised to allow participants to continue treatment for up to a total duration of 2 years.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities; Table 2-2, Baseline for Re-randomization Procedural Outline; Section 3.1.1.2, Specific Attributes of the FRACTION Program Design; Section 5.1, Overall Design; Section 5.1.1, FRACTION-RCC Tracks 1 and 2 Design; Figure 5.1.1-1, Tracks 1 and 2 Study Design Schematic; Section 5.1.3.2, Treatment; Section 5.1.3.3, Follow-up; Section 5.4.1, Rationale for Duration of Therapy	Participants will receive treatment up to 2 years total duration.	Emerging data suggests that patients may derive clinical benefit beyond 6 months of immunotherapy. Therefore, patients will continue on study treatment for up to 2 years.
Table 2-1, Screening Procedural Outline	1. Duration of randomization prior to first dose extended	1. To allow patients to complete all the post randomization procedures required for a sub-protocol, duration between randomization and start of treatment can be extended from to allow for completion of study related tests.
	2. Data to be collected on toxicities from treatment with prior immunotherapies.	2. For patients previously treated with PD-1/PD-L1/CTLA-4, enrolling directly into Track 2, we will collect additional data on details of prior toxicities.
Table 2-3, Follow-up Procedural Outline	Karnofsky Performance Status assessment added at Follow-up visits 2 and 3	Collect performance status during follow-up.
Section 3.1, Introduction; Section 3.2.1, FRACTION-RCC	Included updates from recent clinical studies.	Most recent results of studies provided.
Throughout	Minor rewording/re-formatting for clarification.	Minor, therefore have not been summarized.