Official Title of Study:

A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cobazantinib Versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma

NCT Number: NCT03141177

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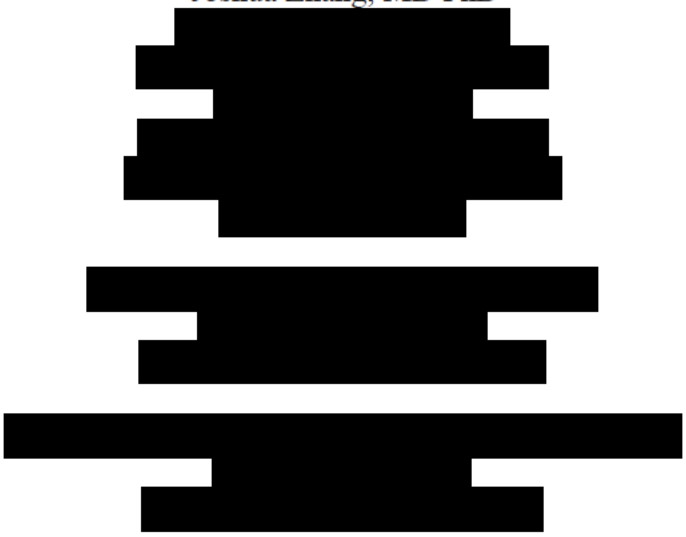
Clinical Protocol CA2099ER

A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma

(CheckMate 9ER: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9ER)

Revised Protocol Number: 02
Incorporates Administrative Letter(s): 02

Study Director/ Medical Monitor
Joshua Zhang, MD PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	03-May-2019	Major Changes: • Revised protocol 02 adjusts the timing of the PFS and OS interim analyses with modified hypothesized OS hazard ratio (HR). The number of randomized participants is increased. • The interim analysis for ORR is removed, resulting in revised overall alpha for PFS and OS endpoints. • No change in eligibility or study procedure. • Clinical data for nivolumuab + ipilimumab in renal cell carcinoma (RCC) has been updated. Other changes include more detail on PRO measures and updates to align with BMS standards for the nivolumab program.
Administrative Letter 02	08-Feb-2018	Clarification to the sites on the implementation of CA2099ER Global Revised Protocol 01 which stopped further randomization into Arm B, and the timing of IRB approval and impact on randomization. Protocol text was not changed.
Revised Protocol 01	18-Dec-2017	Primary revisions: (i) To stop enrollment into Arm B (nivolumab, ipilimumab and cabozantinib triplet) and (ii) to include favorable risk participants (capped at 25%) in the primary data analysis. Secondary items include: (i) to add a Data Monitoring Committee review after 30 participants are treated for 6 weeks, (ii) to adjust, clarify and add exclusion criteria, (iii) to add treatment restrictions, (iv) to clarify criteria associated with hemorrhage with regard to resuming treatment, (v) to specify an additional precaution when sunitinib dosing is resumed, and (vi) to apply newly updated Sponsor standards for nivolumab clinical protocols. Tertiary items include (i) incorporation of Administrative Letter 01 and (ii) correction of typographical and grammatical errors.
Administrative Letter 01	20-Jul-2017	To notify of a change of Medical Monitor and Study Director. To correct typographical errors and resolve inconsistencies found in the original protocol.
Original Protocol	08-Mar-2017	Not applicable

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02

Section Number & Title	Description of Change
Synopsis, Exclusion Criteria 6.2 Exclusion Criteria (2h)	Added exclusion for live/attenuated vaccine
Synopsis, Objectives and Endpoints Table 4.1 Objectives and Endpoints Table 10.3.1-1 Efficacy Analyses	Added text to statistical analysis description of PFS
Synopsis, Overall Design 5.1 Overall Design	The total number of randomized participants is changed from approximately 580 to 638 participants (from 290 to 319 per arm for Arm A and C) and from 434 to 478 for intermediate/poor risk participants
Synopsis, Number of Participants 5.2 Number of Participants	The total number of participants enrolled is changed from 774 to 850 as well as the number of randomized participants per arm A and C
Table 4-1 Objectives and Endpoints	[redacted]
5.1.1 Data Monitoring Committee and Other External Committees 10.1 Sample Size Determination 10.3.4. Interim Analyses	Deleted ORR endpoint Deleted text and table on ORR endpoint Deleted first paragraph in 10.3.4

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02

Section Number & Title	Description of Change
6.2 Exclusion Criteria (5a) 8.1 Discontinuation from Study Treatment	Added "only in countries where local regulations permit"
7.7.1 Prohibited and/or Restricted Treatments	Added prohibition for live/attenuated vaccine
[redacted]	[redacted]
10.1 Sample Size Determination Table 10.1-1 Summary of Sample Size Parameters and Schedule of Analyses Table 10.3.1-1 Efficacy Analyses 10.3.4. Interim Analyses	Removed early assessment of ORR, so overall alpha for PFS and OS endpoints is revised from 0.049 to 0.05 Accrual duration (and accruals per months) are updated from 15 months to 19 months Added requirements for minimal follow-up time of all randomized participant and minimal numbers of events required for final PFS and the 2 interim OS analyses Revised OS hypothesized HR assumption from 0.76 to 0.70. The overall power for OS is therefore increased to 80% Accordingly, the accruals, the number of events, HRs, the timing of analyses, the power for PFS and OS are updated in the correspondent sections and table 10.3.1-1 Deleted first paragraph of 10.3.4
10.3.3.1 Outcomes Research Analyses Table 10.3.3.1-1 Thresholds Values for Change Scores Judged to be Important to Patients	Added new subsection and table
Appendix 2 Study Governance Consideration	Slightly modified definition of "serious breach"; provided additional criteria for the CSR Signatory Investigator; added publication policy
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Revised section on Highly Effective Methods That Are User Independent

[redacted]

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma

Study phase: 3

Study Population: Male and female participants ≥ 18 years or the age of majority with previously untreated, advanced or metastatic renal cell carcinoma (RCC).

The following list contains key eligibility criteria only. For full list of eligibility criteria please see Section 6.

Key Inclusion Criteria

- Histological confirmation of RCC with a clear-cell component, including participants who may also have sarcomatoid features
- Advanced (not amenable to curative surgery or radiation therapy) or metastatic (American Joint Committee on Cancer [AJCC] Stage IV) RCC
- No prior systemic therapy for RCC with the following exception:
    - One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy
- Karnofsky Performance Status (KPS) grade ≥ 70%
- Measurable disease as per RECIST v1.1 per investigator
- Tumor tissue, preferably obtained within 3 months but no more than 12 months prior to enrollment, with an associated pathology report, must be received by the central laboratory during screening for determination of PD-L1 expression. In order to be randomized, a participant must be classified as PD-L1 expression ≥ 1%, PD-L1 expression < 1%, or PD-L1 expression indeterminate.

- Participants with favorable, intermediate, and poor risk categories will be eligible for the study. Participants must be categorized according to favorable versus intermediate versus poor risk status at registration as per International Metastatic RCC Database Consortium (IMDC) criteria.
- Negative pregnancy test and able to meet protocol-specified reproductive requirements

Key Exclusion Criteria

- Any active central nervous system (CNS) metastases. Participants with treated, stable CNS metastases for at least 1 month are eligible
- Any tumor invading the superior vena cava (SVC), other major blood vessels, or GI tract; any evidence of endotracheal or endobronchial tumor
- Prior systemic treatment with VEGF, MET, AXL, KIT or RET targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, sorafenib, lenvatinib, bevacizumab, and cabozantinib)
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Any active, known or suspected autoimmune disease or any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization
- Uncontrolled adrenal insufficiency
- Poorly controlled hypertension despite antihypertensive therapy
- History of unstable angina, myocardial infarction, symptomatic peripheral vascular disease, congestive heart failure (CHF, Class III or IV as defined by the New York Heart Association [NYHA]), or cerebrovascular accident (CVA)
- Deep vein thrombosis (DVT) or pulmonary embolism (PE) unless adequately treated with low molecular weight heparin (LMWH)
- Any unstable cardiac arrhythmia; prolonged QTcF > 450 msec for males and > 470 msec for females
- Serious, non-healing wound or ulcer; evidence of active bleeding or bleeding susceptibility; history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel or gastric outlet obstruction
- Concomitant strong CYP3A4 inducers or inhibitors within 14 days prior to randomization
- Ejection fraction ≤ 50% on screening echocardiogram or multigated acquisition scan (MUGA)
- Major surgery less than 6 weeks, nephrectomy less than 4 weeks, prior to randomization, with complete wound healing and no ongoing post-operative complications.
- Participants who have received a live/attenuated vaccine within 30 days of first treatment.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To compare progression-free survival (PFS) per blinded independent central review (BICR) of nivolumab plus cabozantinib (Arm A, doublet) with sunitinib (Arm C) in all randomized participants.	The primary endpoint of this study is to compare the PFS per BICR of Arm A versus Arm C in all randomized participants. PFS is defined as the time between the date of randomization and the first date of the documented progression, or death due to any cause, whichever occurs first. Participants who die without a reported progression (and die without start of subsequent anti-cancer therapy) will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment on or prior to initiation of subsequent anti-cancer therapy. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of first subsequent anti-cancer therapy.
Secondary	
To compare overall survival (OS) of Arm A with Arm C in all randomized participants.	The first secondary endpoint is to compare the OS of Arm A versus Arm C in all randomized participants. OS is defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died will be censored at the last known alive date.
To evaluate the objective response rate (ORR) per BICR in-all randomized participants.	The second secondary endpoint is to describe ORR per BICR in all randomized participants. ORR is defined as the proportion of randomized participants who achieve a best response of complete response (CR) or partial response (PR) using the RECIST 1.1 criteria. Best overall response (BOR) is defined as the best response designation recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Duration of response (DOR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last tumor assessment. Responders who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anti-cancer therapy. Time to response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by BICR. DOR and TTR will be evaluated for responders (CR or PR) only.
To assess overall safety and tolerability in all treated participants.	As measured by the incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, deaths, laboratory abnormalities and changes from baseline.

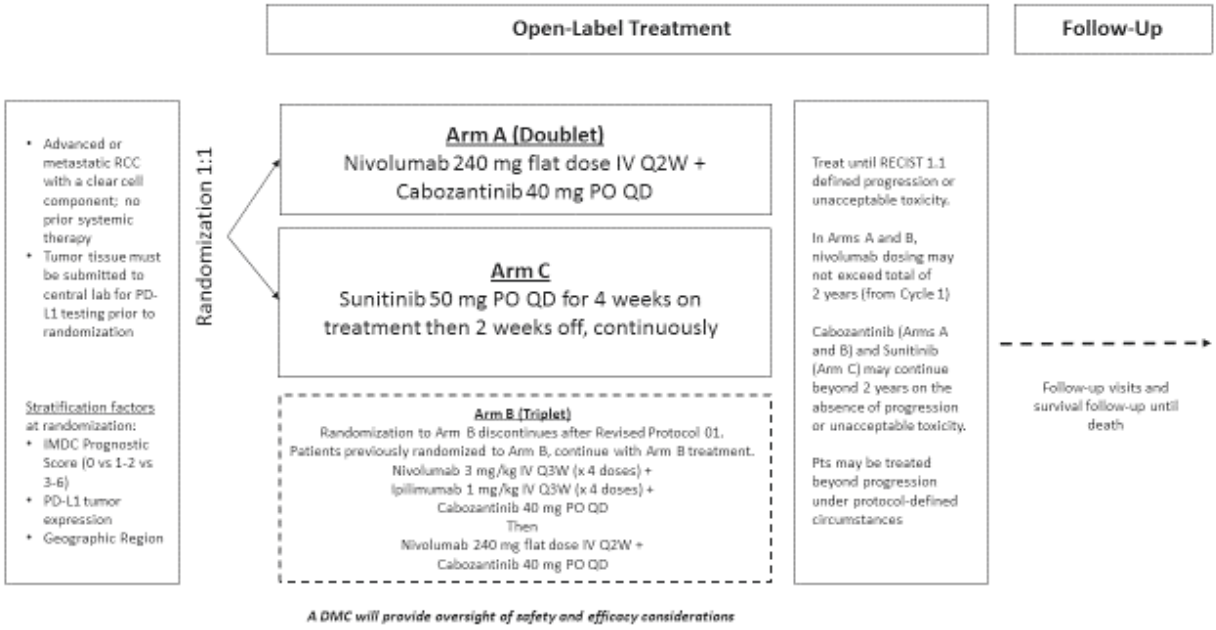
Overall Design:

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

This is an open label, randomized trial of nivolumab combined with cabozantinib (doublet regimen) versus sunitinib in participants with previously untreated (first line) advanced or metastatic RCC. Participants will be randomized between Arm A and Arm C in a 1:1 ratio with approximately 638 participants (319 per Arms A and C, respectively), and capped at 25% favorable risk participants. Participants will be stratified for randomization by IMDC prognostic score (0 [favorable risk] versus 1-2 [intermediate risk] versus 3-6 [poor risk]), PD-L1 tumor expression (≥ 1% versus < 1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe versus rest of the world [ROW]).

The study design schematic is presented below.



Abbreviations: DMC= data monitoring committee; IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; IV=intravenous;; PD-L1= programmed death-ligand 1; PO= orally by mouth; Pts=participants; Q2W=every 2 weeks; Q3W=every 3 weeks; QD= once daily; RCC=renal cell carcinoma.

Arm B is shown in the design schematic because after implementation of Revised Protocol 01, there will be patients on Arm B treatment from the original protocol version 08 Mar 2017.

Number of Participants: Approximately 850 participants will enroll in order to randomize 638 participants into Arms A and C (319 per Arm A and per Arm C) capped at 25% favorable risk participants.

Treatment Arms and Duration:

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

- Arm A (Doublet): Nivolumab 240 mg flat dose intravenously (IV) every 2 weeks (Q2W) + Cabozantinib 40 mg orally by mouth (PO) once daily (QD)
    - Nivolumab treatment until disease progression or unacceptable toxicity with maximum treatment of 2 years
    - Cabozantinib treatment until disease progression or unacceptable toxicity
- Arm C: Sunitinib 50 mg PO QD for 4 weeks, followed by 2 weeks off-treatment, per cycle. Cycles to be continued until progression or unacceptable toxicity

Note - Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

- Arm B (Triplet): Nivolumab 3mg/kg IV Q3W x 4 doses + Ipilimumab 1 mg/kg IV Q3W x 4 doses + Cabozantinib 40 mg PO QD
    - Then, Nivolumab 240 mg flat dose IV Q2W + Cabozantinib 40 mg PO QD
    - Nivolumab to be continued until disease progression or unacceptable toxicity with maximum treatment of 2 years from the start of first dose in Cycle 1
    - Cabozantinib until disease progression or unacceptable toxicity

Refer to Section 7.1 Treatments Administered for additional details.

Study treatment:

Study Drugs for CA2099ER

Medication	Potency	IP/ Non-IP
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection*	200 mg (5 mg/mL)	IP
Cabozantinib Tablet	20 mg	IP
Sunitinib Malate Capsule	12.5 mg	IP

Abbreviation: IP=investigational product

*Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099ER)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain participant number. The participant should sign the Informed consent prior to any study related assessment is performed.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	
International Metastatic RCC Database Consortium (IMDC) Prognostic Score	X	See Appendix 6.
Tumor tissue sample (for stratification by PD-L1 tumor expression)	X	Tumor tissue (preferably obtained within 3 months but no more than 12 months prior to enrollment, with an associated pathology report) will be collected. Formalin-fixed paraffin-embedded (FFPE) block or 20 unstained slides: a minimum of 10 slides will be acceptable if tumor tissue is limited. See Section 9.8.2. Central lab will determine PD-L1 tumor expression. Participants must have an evaluable PD-L1 result from the central lab in order to be randomized.
Safety Assessments		
Full Physical Examination, Measurements, Vital Signs, and Performance Status	X	Height, weight, Karnofsky Performance Status (KPS) (Appendix 7), BP, HR, RR, and temperature within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
[redacted]	[redacted]	[redacted]
Serious Adverse Events Assessment	X	Serious Adverse Events from time of consent. See Section 9.2
Electrocardiogram (ECG)	X	Within 28 days prior to randomization. Fridericia corrected QT (QTcF) required. If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.

Table 2-1: Screening Procedural Outline (CA2099ER)

Procedure	Screening Visit[a]	Notes
Cardiac Ejection Fraction (via Echocardiogram or MUGA)	X	Within 28 days prior to randomization.
Laboratory Tests (includes blood and urine samples)	X	See Section 9.4.1 for additional details on tests required. To be completed locally at each site. Must be performed within 14 days prior to randomization. • CBC w/differential • PT/INR, PTT • Chemistry panel (includes AST, ALT, total bilirubin, ALP, LDH, creatinine, BUN, glucose, albumin, Na, K, Cl, Ca (also corrected), P, Mg, amylase, lipase) • Thyroid panel (includes TSH with free T3 and free T4) • Hepatitis B/C (HBVsAg, HCV antibody or HCV RNA) • HIV if mandated locally (sites in Germany, see Appendix 12) • Urine protein and urine creatinine (for urine protein/creatinine ratio [UPCR]). If UPCR ≥ 1.0, obtain 24 hour urine protein.
Pregnancy Test	X	WOCBP only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy.
Follicle Stimulating Hormone (FSH)	X	For women under the age of 55 years to confirm menopause as needed.
Efficacy Assessments		
Baseline Tumor Assessments	X	CT/MRI of the chest, abdomen, pelvis, brain, and all known sites of disease, performed within 28 days prior to randomization. All scans need to be submitted for blinded independent central review (BICR). See Section 9.1.

Abbreviations: For abbreviations on lab tests refer back to Section 9.4.1.

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-2: On Treatment Procedural Outline for Arm A Nivolumab Combined with Cabozantinib, Doublet (CA2099ER)

Procedure	Cycle 1, Day 1 Cycle=2 wks	C2 and subsequent visits[a] Each Cycle=2 wks	Notes
Safety Assessments			
Targeted Physical Examination, Vital Signs, Performance Status	X	X	Weight, BP, HR, RR, temperature, and Karnofsky Performance Status (KPS) (Appendix 7). Performance Status to be performed within 72 hours prior to dosing.
Assessment of Signs and Symptoms	X	X	
Adverse Events and Serious Adverse Events Assessment	X	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose (Appendix 3).
[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram (ECG)	X	X (See notes)	Fridericia corrected QT (OTcF) required. Only for Cycles 1, 4, 7, then every 6 cycles (ie, Cycles 13, 19, 25, etc). If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.
Laboratory Tests (includes blood and urine samples)	X	X (See notes)	See 9.4.1 for additional details on tests required. Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to first dose. After C1D1, within 72 hours prior to dosing: • CBC w/differential at every cycle • Chemistry panel at every cycle (includes AST, ALT, total bilirubin, ALP, LDH, creatinine, BUN, glucose, albumin, Na, K, Cl, Ca, P, Mg) • Amylase and lipase to be done for Cycles, 1, 2, 4, 5, 7, and then every 3 cycles (ie, Cycles 10, 13, 16, etc) • Thyroid panel (includes TSH with reflexive free T3 and free T4) for Cycles 1, 2, 4, 5, 7, and then every 3 cycles (ie, Cycles 10, 13, 16, etc) • Urine protein and urine creatinine (for UPCR, preferred) or urine dipstick for protein every 3 cycles (ie, Cycles 1, 4, 7, 10, etc).

Table 2-2: On Treatment Procedural Outline for Arm A Nivolumab Combined with Cabozantinib, Doublet (CA2099ER)

Procedure	Cycle 1, Day 1 Cycle=2 wks	C2 and subsequent visits[a] Each Cycle=2 wks	Notes
Pregnancy Test	X	X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 7 days. Serum or Urine. WOCBP only.
Efficacy Assessments			
Tumor Assessments	First tumor assessment post-baseline should be performed Week 12 (± 7 days) following randomization. Use same imaging method as was used at baseline. Subsequent tumor assessments should occur at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator and confirmed by the BICR.		CT/MRI of the chest, abdomen, pelvis, and all known sites of disease. Tumor assessments should be performed at the specified time points regardless of dosing delays. See Section 9.1 for additional details. Treatment Beyond Progression A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression. Refer to Section 8.1.4 for tumor assessment associated with Treatment beyond progression.
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 2-2: On Treatment Procedural Outline for Arm A Nivolumab Combined with Cabozantinib, Doublet (CA2099ER)

Procedure	Cycle 1, Day 1 Cycle=2 wks	C2 and subsequent visits[a] Each Cycle=2 wks	Notes
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
Participant-Reported Outcomes			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Health Care Resource Utilization	X	X	See Section 9.9.
Study Treatment			

Table 2-2: On Treatment Procedural Outline for Arm A Nivolumab Combined with Cabozantinib, Doublet (CA2099ER)

Procedure	Cycle 1, Day 1 Cycle=2 wks	C2 and subsequent visits[a] Each Cycle=2 wks	Notes
Randomize	X		Begins with call to Interactive Response Technology (IRT). Participants must have an evaluable PD-L1 result from the central lab in order to be randomized.
Administer Nivolumab and Cabozantinib	X	X	See Section 7. Dispense study treatment as appropriate. Day 1 Treatment must begin within 3 days (72 hours) of Randomization)

Abbreviations: C=cycle; D=day; wks= weeks. For abbreviations on lab tests refer back to Section 9.4.1.

Notes: Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

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

Table 2-3: On Treatment Procedural Outline for Arm B Nivolumab and Ipilimumab Combined with Cabozantinib, Triplet (CA2099ER)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

Procedure	Part 1		Part 2	Notes (Please note differences in cycle durations between Part 1 and Part 2)
	Cycle 1 (Each Cycle=3 wks)	C2-C4[a] (Each Cycle= 3 wks)	C5 and Subsequent visits [a] (Each Cycle=2 wks)	
Safety Assessments				
Targeted Physical Examination, Vital Signs, Performance Status	X	X	X	Weight, BP, HR, RR, temperature, and Karnofsky Performance Status (KPS) (Appendix 7). Performance Status to be performed within 72 hours prior to dosing.
Assessment of Signs and Symptoms	X	X	X	
Adverse Events and Serious Adverse Events Assessment	X	X	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose (Appendix 3).
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram (ECG)	X	X (See notes)	X (See notes)	Fridericia corrected QT (QTcF) required. Only Cycles 1, 3, 5, then every 6 cycles (ie, Cycles 11, 17, 23, etc). If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.
Laboratory Tests (includes blood and urine samples)	X	X	X (See notes)	See Section 9.4.1 for additional details on tests required. Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to first dose. After C1D1, within 72 hours prior to dosing. • CBC w/differential at every cycle

Table 2-3: On Treatment Procedural Outline for Arm B Nivolumab and Ipilimumab Combined with Cabozantinib, Triplet (CA2099ER)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

Procedure	Part 1		Part 2	Notes (Please note differences in cycle durations between Part 1 and Part 2)
	Cycle 1 (Each Cycle=3 wks)	C2-C4[a] (Each Cycle= 3 wks)	C5 and Subsequent visits [a] (Each Cycle=2 wks)	
				• Chemistry panel at every cycle (includes AST, ALT, total bilirubin, ALP, LDH, creatinine, BUN, glucose, albumin, Na, K, Cl, Ca, P, Mg) • Amylase and lipase at every cycle until Cycle 5 then every 3 cycles (ie, Cycles 8, 11, 14, etc) • Thyroid panel (includes TSH with reflexive free T3 and free T4) at every cycle until Cycle 5, then every 3 cycles (ie, Cycles 8, 11, 14, etc) • Urine protein and urine creatinine (for UPCR, preferred) or urine dipstick for protein at Cycles 1, 3, and 5, then every 3 cycles (ie, Cycles 8, 11, 14, etc)
Pregnancy Test	X	X	X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 7 days. Serum or Urine. WOCBP only.
Efficacy Assessments				
Tumor Assessments	First tumor assessment post-baseline should be performed Week 12 (± 7 days) following randomization. Use same imaging method as was used at baseline. Subsequent tumor assessments should occur at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator and confirmed by the BICR.			CT/MRI of the chest, abdomen, pelvis, and all known sites of disease. Tumor assessments should be performed at the specified time points regardless of dosing delays. See Section 9.1 for additional details. Treatment Beyond Progression A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression. Refer to Section 8.1.4 for tumor assessment associated with Treatment beyond progression.

Table 2-3: On Treatment Procedural Outline for Arm B Nivolumab and Ipilimumab Combined with Cabozantinib, Triplet (CA2099ER)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

Procedure	Part 1		Part 2	Notes (Please note differences in cycle durations between Part 1 and Part 2)
	Cycle 1 (Each Cycle=3 wks)	C2-C4[a] (Each Cycle= 3 wks)	C5 and Subsequent visits [a] (Each Cycle=2 wks)	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
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[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]

Table 2-3: On Treatment Procedural Outline for Arm B Nivolumab and Ipilimumab Combined with Cabozantinib, Triplet (CA2099ER)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

Procedure	Part 1		Part 2	Notes (Please note differences in cycle durations between Part 1 and Part 2)
	Cycle 1 (Each Cycle=3 wks)	C2-C4[a] (Each Cycle= 3 wks)	C5 and Subsequent visits [a] (Each Cycle=2 wks)	
[redacted]	[redacted]			[redacted]
Participant-Reported Outcomes				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health Care Resource Utilization	X	X	X	See Section 9.9.
Study Treatment				

Table 2-3: On Treatment Procedural Outline for Arm B Nivolumab and Ipilimumab Combined with Cabozantinib, Triplet (CA2099ER)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

Procedure	Part 1		Part 2	Notes (Please note differences in cycle durations between Part 1 and Part 2)
	Cycle 1 (Each Cycle=3 wks)	C2-C4[a] (Each Cycle= 3 wks)	C5 and Subsequent visits [a] (Each Cycle=2 wks)	
Randomize	X			Begins with call to Interactive Response Technology (IRT). Participants must have an evaluable PD-L1 result from the central lab in order to be randomized. Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B (Triplet) continue with Arm B treatment and continue with Arm B clinically planned events, per protocol.
Administer Nivolumab, Ipilimumab, and Cabozantinib	X	X		Cycles 1 to 4 are 3 week cycles. See Section 7. Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B (Triplet) continue with Arm B treatment and continue with Arm B clinically planned events, per protocol.
Administer Nivolumab and Cabozantinib			X	Day 1 Treatment must begin within 3 days (72 hours) of Randomization) Cycle 5 and subsequent cycles are 2 week cycles. See Section 7.
Dispense Study Treatment	X	X	X	See Section 7.

Abbreviations: C=cycle; D=day; wks= weeks. For abbreviations on lab tests refer back to Section 9.4.1.

Notes: Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

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

Table 2-4: On Treatment Procedural Outline for Arm C Sunitinib (CA2099ER)

Procedure	Cycle 1 Each Cycle=6wks		Cycle 2 [a] Each Cycle=6 wks		C3 and Subsequent visits[a] Each Cycle=6 wks		Notes
	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	
Safety Assessments							
Targeted Physical Examination, Vital Signs, Performance Status	X		X		X		Weight, BP, HR, RR, temperature, and Karnofsky Performance Status (KPS) (Appendix 7). Performance Status to be performed within 72 hours prior to dosing.
Assessment of Signs and Symptoms	X	X	X	X	X	X	
Adverse Events and Serious Adverse Events Assessment	X	X	X	X	X	X	Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose (Appendix 3).
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram (ECG)	X		X		X (See notes)		Fridericia corrected QT (QTcF) required. Only Cycles 1, 2, and 3, then every 2 cycles (ie, Cycles 5, 7, 9, etc). If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.
Laboratory Tests (includes blood and urine samples)	X	X (See notes)	X	X (See notes)	X	X (See notes)	See Section 9.4.1 for additional details on tests required. Laboratory tests do not need to be repeated at C1D1 if performed within 14 days prior to first dose. After C1D1, within 72 hours prior to specified dosing day: • CBC w/differential on Day 1 and Day 22 (+/- 3 days) of each cycle

Table 2-4: On Treatment Procedural Outline for Arm C Sunitinib (CA2099ER)

Procedure	Cycle 1 Each Cycle=6wks		Cycle 2 [a] Each Cycle=6 wks		C3 and Subsequent visits[a] Each Cycle=6 wks		Notes
	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	
							• Chemistry panel on Day 1 and Day 22 (+/- 3 days) of every cycle (includes AST, ALT, total bilirubin, ALP, LDH, creatinine, BUN, glucose, albumin, Na, K, Cl, Ca, P, Mg) • Amylase and lipase on Day 1 and Day 22 (+/- 3 days) of Cycle 1 and 2, then on Day 1 of Cycle 3 and all subsequent cycles. • Thyroid panel (includes TSH with reflexive free T3 and free T4) on Day 1 and Day 22 (+/- 3 days) of Cycle 1 and 2, then on Day 1 of Cycle 3 and all subsequent cycles. • Urine protein and urine creatinine (for UPCR, preferred) or urine dipstick for protein on Day 1 of every cycle
Pregnancy Test	X	X	X	X	X	X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 7 days. Serum or Urine. WOCBP only.
Efficacy Assessments							
Tumor Assessments	First tumor assessment post-baseline should be performed Week 12 (± 7 days) following randomization. Use same imaging method as was used at baseline. Subsequent tumor assessments should occur at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator and confirmed by the BICR.						CT/MRI of the chest, abdomen, pelvis, and all known sites of disease. Tumor assessments should be performed at the specified time points regardless of dosing delays. See Section 9.1 for additional details. Treatment Beyond Progression A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed

Table 2-4: On Treatment Procedural Outline for Arm C Sunitinib (CA2099ER)

Procedure	Cycle 1 Each Cycle=6wks		Cycle 2 [a] Each Cycle=6 wks		C3 and Subsequent visits[a] Each Cycle=6 wks		Notes
	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	
							progression. Refer to Section 8.1.4 for tumor assessment associated with Treatment beyond progression.
[redacted]							
[redacted]	[redacted]						[redacted]
[redacted]	[redacted]		[redacted]				[redacted]
[redacted]	[redacted]		[redacted]				[redacted]
[redacted]	[redacted]						[redacted]
[redacted]	[redacted]		[redacted]				[redacted]
[redacted]	[redacted]						[redacted]

Table 2-4: On Treatment Procedural Outline for Arm C Sunitinib (CA2099ER)

Procedure	Cycle 1 Each Cycle=6wks		Cycle 2 [a] Each Cycle=6 wks		C3 and Subsequent visits[a] Each Cycle=6 wks		Notes
	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	Day 1	Day 22 (+/- 3 days)	
Participant-Reported Outcomes							
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]
Health Care Resource Utilization	X		X		X		See Section 9.9.
Study Treatment							
Randomize	X						Begins with call to Interactive Response Technology (IRT). Participants must have an evaluable PD-L1 result from the central lab in order to be randomized.
Administer Sunitinib	X	X	X	X	X	X	Day 1 Treatment must begin within 3 days (72 hours) of Randomization) Each cycle will be 6 weeks where sunitinib will be administered for 4 weeks, then participants will be off treatment for 2 weeks. See Section 7.
Dispense Study Treatment	X		X		X		See Section 7.

Abbreviations: C=cycle; D=day; wks= weeks. For abbreviations on lab tests refer back to Section 9.4.1.

Notes: Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

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

Table 2-5: Follow-Up Procedural Outline for All Arms (CA2099ER)

Procedure	Safety Follow-up (Follow up Visit 1 (FU1) and Visit 2 (FU2)[a]	Survival Follow-up[b]	Notes
Safety Assessments			
Targeted Physical Examination, Vital Signs, Performance Status	X		Weight, BP, HR, RR, temperature, and Karnofsky Performance Status (KPS) (Appendix 7).
Assessment of Signs and Symptoms	X		
Adverse Events and Serious Adverse Events Assessment	X		Record at each visit. Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose (Appendix 3).
[redacted]	[redacted]		[redacted]
Electrocardiogram (ECG)	X		Fridericia corrected QT (QTcF) required. If any time there is an increase in QTcF interval to an absolute value > 500 msec, 2 additional ECGs must be performed each with intervals approximately 3 minutes apart.
Laboratory Tests (includes blood and urine samples)	FU1 -yes FU2 - if toxicities are present		See Section 9.4.1 for additional details on tests required. • CBC w/differential, PT/INR, and PTT • Chemistry panel (includes AST, ALT, total bilirubin, ALP, LDH, creatinine, BUN, glucose, albumin, Na, K, Cl, Ca, P, Mg, amylase, lipase) • Thyroid panel (includes TSH with reflexive free T3 and free T4) • Urine protein and urine creatinine (for UPCR, preferred) or urine dipstick for protein
Pregnancy Test	X		Serum or Urine. WOCBP only.
Efficacy Assessments			
Tumor Assessments	First tumor assessment post-baseline should be performed Week 12 (± 7 days) following randomization. Use same imaging method as was used at baseline.		Participants who discontinue study treatment without radiographic progression, confirmed by BICR, will continue tumor assessments according to the protocol specified schedule, even if new anti-tumor therapy has been initiated in the Follow-Up phase, until radiographic

Table 2-5: Follow-Up Procedural Outline for All Arms (CA2099ER)

Procedure	Safety Follow-up (Follow up Visit 1 (FU1) and Visit 2 (FU2)[a]	Survival Follow-up[b]	Notes
	Subsequent tumor assessments should occur at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator and confirmed by the BICR.		progression has been assessed by the investigator and confirmed by BICR. CT/MRI of the chest, abdomen, pelvis, and all known sites of disease. See Section 9.1.2 for additional details.
Survival Status	X	X	During safety follow up and every 3 months (clinic visit or by telephone) during survival phase. Include documentation of subsequent chemotherapy. See Section 8.1.5.
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
Participant-Reported Outcomes			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Health Care Resource Utilization	X		See Section 9.9.

Abbreviations: C=cycle; wks= weeks; FU= follow up. For abbreviations on lab tests, see Section 9.4.1.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 (FU1) should occur 30 days from the last dose (+/- 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up visit #2 (FU2) occurs approximately 100 days (+/- 7 days) from last dose of study drug. Both Follow Up visits should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months from Follow-up Visit #2. Survival visits may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

3 INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common cancer in the world with an increasing incidence.[1] Globally, RCC occurs in more than 330,000 cases with approximately a third of the patients succumbing to their disease. More than 100,000 deaths occur annually, as a result of progression of metastatic disease. Despite the earlier detection of smaller kidney tumors, the rate of RCC-related mortality has increased suggesting that recurrence and advanced disease are responsible for mortality.[2,3] With the rise in RCC incidence, as well as mortality and morbidity associated with advanced RCC, medical need in this population remains a priority.

Over the last decade, an increased understanding of the biology of RCC has led to development of multiple agents that target specific growth pathways. The vascular endothelial growth factor (VEGF) pathway and targeted serine/threonine protein kinase therapies that block the mammalian target of rapamycin (mTOR) have been found to be important targets in RCC disease. Global health authorities (HAs) have approved multiple drugs targeting these pathways, including anti-VEGF agents, such as pazopanib, sorafenib, sunitinib, cabozantinib, and bevacizumab, and mTOR pathway inhibitors, such as temsirolimus and everolimus.[4] Additionally, recent innovation of treating cancer with immunotherapies has also expanded treatment options. Nivolumab, an anti-PD-1 antibody, given as monotherapy or in combination with the anti-CTLA-4 antibody, ipilimumab, has demonstrated clinical activity in multiple tumor types, including RCC.

To better understand treatment and patient outcomes, several academic groups have identified variables associated with survival and created prognostic models in mRCC. These risk models are commonly used for choosing therapies or selecting patients for treatment in clinical trials. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model stratifies patients into 3 prognostic groups, based on 6 adverse prognostic factors, into favorable (0 factors), intermediate (1-2 factors), and poor risk (3-6 factors) groups.[5] The currently available first-line agents for mRCC, which target the VEGF pathway, have shown limited efficacy in the intermediate and poor risk populations, yielding median overall survival of approximately 2 years or less.

Cabozantinib and nivolumab both share category 1 NCCN guideline recommendations (ie, uniform consensus that the treatment is appropriate, based on high-level evidence) for the treatment of previously treated mRCC patients.[6] Therefore, it is an appropriate next step to combine these agents and move them to the first-line setting in an attempt to improve clinical outcomes in patients with advanced RCC. This protocol CA2099ER will test the clinical activity of nivolumab combined with cabozantinib (doublet regimen). Given the different mechanisms of action of each of these agents, there is potential for distinct improvement in clinical efficacy.[7]

[redacted]

3.1.1 Research Hypothesis

Treatment with nivolumab combined with cabozantinib (doublet regimen) will demonstrate an improvement in PFS per BICR compared to sunitinib monotherapy in participants with previously untreated mRCC.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
To compare progression-free survival (PFS) per BICR of nivolumab combined with cabozantinib (Arm A: doublet) with sunitinib (Arm C) in all randomized participants.	The primary endpoint of this study is to compare PFS per BICR of Arm A versus Arm C in all randomized participants. PFS is defined as the time between the date of randomization and the first date of the documented progression, or death due to any cause, whichever occurs first. Participants who die without a reported progression (and die without start of subsequent anti-cancer therapy) will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment on or prior to initiation of subsequent anti-cancer therapy. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of first subsequent anti-cancer therapy.
Secondary	
To compare overall survival (OS) of Arm A with Arm C in all randomized participants.	The first secondary endpoint is to compare OS of Arm A versus Arm C in all randomized participants. OS is defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died will be censored at the last known alive date.
To evaluate the objective response rate (ORR) per BICR in all randomized participants.	The second secondary endpoint is to describe ORR per BICR in all randomized participants. ORR is defined as the proportion of randomized participants who achieve a best response of complete response (CR) or partial response (PR) using the RECIST 1.1 criteria. Best overall response (BOR) is defined as the best response designation recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For participants without document progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Duration of response (DOR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last tumor assessment. Responders who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anti-cancer therapy. Time to response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by BICR. DOR and TTR will be evaluated for responders (CR or PR) only.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
To assess overall safety and tolerability in all treated participants.	As measured by the incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, deaths, laboratory abnormalities and changes from baseline.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5 STUDY DESIGN

5.1 Overall Design

CA2099ER Global Revised Protocol 01

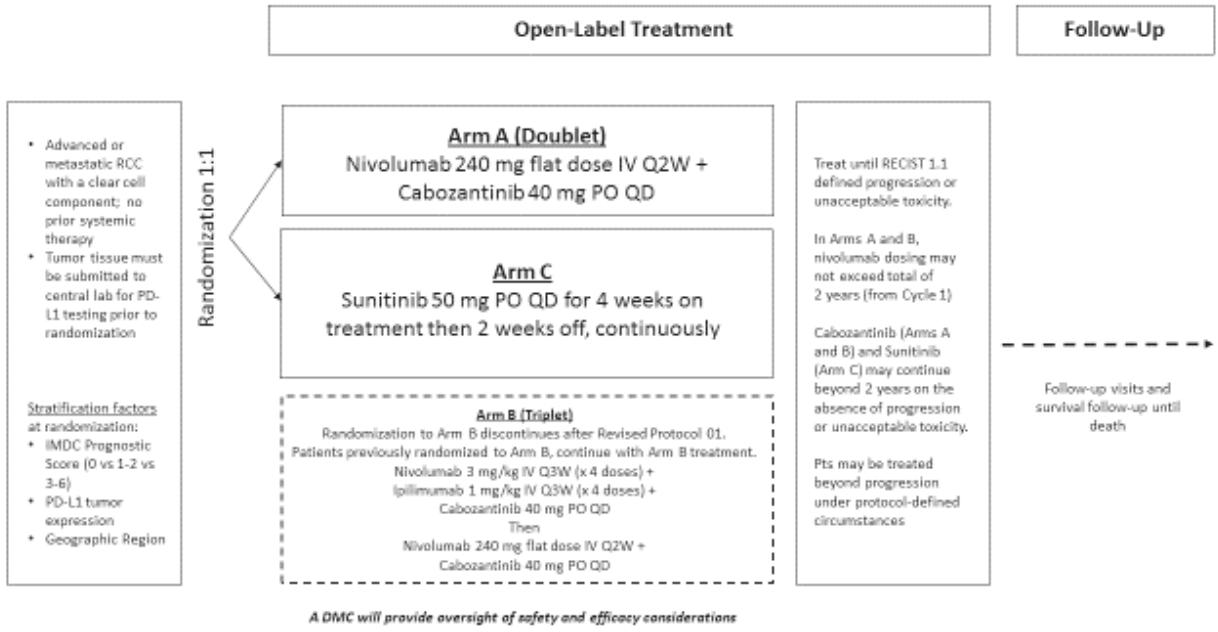
Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

This is an open label, randomized trial of nivolumab combined with cabozantinib (doublet regimen) versus sunitinib in participants with previously untreated (first line) advanced or metastatic RCC. Participants will be randomized between Arm A and Arm C in a 1:1 ratio with approximately 638 participants (319 per arm) capped at approximate 25% to represent the normal frequency of favorable risk group in mRCC. The rest of the randomized participants will provide approximately 478 intermediate/poor risk randomized participants (239 per arm). Participants will be stratified at the time of randomization by IMDC prognostic score (0 [favorable risk] versus-1-

2 [intermediate risk] versus 3-6 [poor risk]), PD-L1 tumor expression (≥ 1% versus < 1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe versus rest of the world [ROW]).

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

Figure 5.1-1: Study Design Schematic



Abbreviations: DMC= data monitoring committee; IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; IV=intravenous; PD-L1= programmed death-ligand 1; PO= orally by mouth; Pts=patients/participants; Q2W=every 2 weeks; Q3W=every 3 weeks; QD= once daily; RCC=renal cell carcinoma.

Arm B is shown in the design schematic because after implementation of Revised Protocol 01, there will be be patients on treatment from the original protocol version 08 Mar 2017.

This study will consist of 3 stages: screening, treatment, and follow up phase.

Screening stage: Screening begins by establishing the participant's initial eligibility and signing of the informed consent (ICF). Sufficient, recent tumor tissue, preferably obtained within 3 months but no more than 12 months prior to enrollment, from a metastatic tumor lesion or from a primary tumor lesion which has not been previously irradiated (formalin-fixed paraffin-embedded block or 20 unstained slides: a minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) will be submitted to the central laboratory. Upon receipt of the tumor sample, the central lab will determine PD-L1 expression level by immunohistochemistry (IHC) testing (see Section 9.8.2). In order to be randomized in the Interactive Response Technology (IRT) system, a participant must be classified as PD-L1 expression ≥ 1%, PD-L1 expression < 1%,

or PD-L1 expression indeterminate. Sites will be informed when the submitted tumor sample is insufficient for PD-L1 testing by the central lab.

Participants will be assessed for complete study eligibility prior to randomization as specified in Section 2.

The Screening stage ends with either confirmation of full eligibility and randomization for the participant or with the confirmation that the participant is a screen failure. This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure prior to randomization. If re-enrolled, the participant must be re-consented. A new participant identification number will be assigned by IRT at the time of re-enrollment.

Treatment stage:

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

The Treatment stage begins when the randomization call is made into the IRT. The participant is randomly assigned to 1 of the 2 treatment arms as noted in the study schematic above.

- Arm A (Doublet): Nivolumab 240 mg flat dose IV Q2W + Cabozantinib 40 mg PO QD
    - Nivolumab to be continued until disease progression or unacceptable toxicity with maximum treatment of 2 years from the first dose in Cycle 1
    - Cabozantinib to be continued until disease progression or unacceptable toxicity
- Arm C: Sunitinib 50 mg PO QD for 4 weeks, followed by 2 weeks off, per cycle. Cycles to be continued until progression or unacceptable toxicity

- Note - Randomization to Arm B stops with implementation of approved CA2099ER Global Revised Protocol 01. Treatment B (below) continues only for participants randomized to Arm B prior to implementation of Global Revised Protocol 01
    - Arm B (Triplet): Nivolumab 3mg/kg IV + Ipilimumab 1 mg/kg IV, both Q3W x 4 doses + Cabozantinib 40 mg PO QD
        - Then Nivolumab 240 mg flat dose IV Q2W + Cabozantinib 40 mg PO QD
        - Nivolumab to be continued until disease progression, unacceptable toxicity, or a maximum of 2 years from the first dose in Cycle 1
        - Cabozantinib to be continued until progression or unacceptable toxicity

Study treatment must begin within 3 days (72 hours) of randomization. Participants in Arm A will continue nivolumab until progression, unacceptable toxicity, withdrawal of consent, or a maximum of 2 years from the first dose in Cycle 1, whichever occurs first. Cabozantinib (Arm A) may be continued until progression, unacceptable toxicity, or withdrawal of consent, whichever occurs first, and may extend beyond 2 years from the first dose in Cycle 1. See Table 7.1-1 and

Table 7.1-2 for the dosing schedule. Study drugs may be delayed for toxicity (See Section 7.4.1). Treatment may be continued beyond investigator-assessed progression if the investigator confirms that the participant meets the criteria specified in Section 8.1.4.

A negative pregnancy test should be documented within 24 hours prior to the initial dose of the investigational product and then performed every 4 weeks ± 7 days during treatment. On-study laboratory assessments should be drawn within 72 hours prior to dosing and will be assessed at the local laboratory.

Tumor assessments will occur in accordance with Section 2 and Section 9.1.2 until progression has been assessed by the investigator **and** confirmed by the blinded independent central review (BICR). Each site must submit scans on a rolling basis, preferably within 7 days of image acquisition, to a third-party vendor for BICR. If progression is assessed by the investigator, the site will inform the radiology vendor so that the BICR assessment of progression can be performed. The BICR assessment of progression will be completed, and the results provided to the site, within approximately 14 days, as specified in Section 9.1.2.

[redacted]

Adverse event assessments should be documented at each clinic visit.

[redacted]

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

Follow-up stage: The Follow-up stage begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy). Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 (FU1) should occur 30 days from the last dose (+/- 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up visit #2 (FU2) occurs approximately 100 days (+/- 7 days) from last dose of study drug. Both Follow Up visits should be conducted in person. AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible. [redacted]

Participants who discontinued study treatment without BICR confirmed radiographic progression will continue to have tumor assessments performed according to the frequency described in Sections 2 and 9.1.2, even if new anti-tumor therapy has been initiated. If progression is assessed by the investigator, the site will inform the radiology vendor, so that the BICR assessment of progression can be performed. Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until BICR confirms progression on a subsequent tumor assessment (See Section 9.1.2.2 for additional details).

After the Follow-up 2 Visit, all participants will be followed for overall survival status every 3 months (+/- 14 days) until death, withdrawal of consent, loss to follow-up, or end of study. Survival status can be ascertained in person or by telephone contact. If new anti-tumor therapy is

initiated for either progression or a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate Case Report Form (CRF).

5.1.1 Data Monitoring Committee and Other External Committees

To provide independent oversight of safety, efficacy, and study conduct, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that participant safety is carefully monitored, including a safety assessment after the first 30 participants are randomized including participants in Arm B prior to global Revised Protocol 01 and are followed for at least 6 weeks and then again after the first 75 participants are randomized and followed for at least 6 weeks. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. The DMC will also review the interim analysis results and inform BMS whether stopping criteria for superiority are met at that time. A separate DMC charter will describe the activities of this committee in more detail.

Blinded independent central review (BICR) will be utilized in this study for determination of PFS endpoint. The BICR will review all available tumor assessment scans for all randomized participants. Details of BICR responsibilities and procedures will be specified in the BICR charter.

5.2 Number of Participants

Approximately 850 participants will be enrolled in order to randomize approximately 638 participants (319 per Arm A and per Arm C). The number of randomized participants with favorable risk disease will be capped at approximately 25% (160) participants.

5.3 End of Study Definition

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

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

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

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

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

i) One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

d) Karnofsky Performance Status (KPS) ≥ 70% (See Appendix 7)

e) Measurable disease as per RECIST v1.1 per investigator. (See Appendix 8)

f) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, preferably obtained within 3 months but no more than 12 months prior to enrollment, with an associated pathology report, must be submitted to the central laboratory during screening. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission. In participants who received prior adjuvant or neoadjuvant therapy, the tumor sample must have been obtained after completion of adjuvant or neoadjuvant therapy. Upon receipt of the tumor sample, the central lab will determine PD-L1 expression level by IHC testing (see Section 9.8.2). In order to be randomized in the IRT system, a participant must be classified as PD-L1 expression ≥ 1%, PD-L1 expression < 1%, or PD-L1 expression indeterminate. Sites will be informed when the submitted tumor sample is insufficient for PD-L1 testing by the central lab.

g) Participants with favorable, intermediate and poor risk categories will be eligible for the study. To be eligible for the Intermediate and Poor-Risk cohort, at least one of the following prognostic factors as per International Metastatic RCC Database Consortium (IMDC) must be present: (See Appendix 6)

i) KPS equal to 70%

ii) Less than 1 year from initial diagnosis (including original localized disease if applicable) to randomization

iii) Hemoglobin < lower limit of normal (LLN)

iv) Corrected calcium concentration > 10 mg/dL

v) Absolute neutrophil count > ULN

vi) Platelet count > ULN

If none of the above factors are present, participants are only eligible for the favorable-risk cohort. Approximately 160 favorable risk participants will be randomized. Enrollment of favorable risk participants may be closed earlier than enrollment for intermediate and poor risk participants.

3) Age and Reproductive Status

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

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately five half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment (ie, 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives).

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Any active CNS metastases. Participants with treated, stable CNS metastases for at least 1 month are eligible as long as they meet the following criteria:

Treated CNS metastases are defined as having no ongoing requirement for corticosteroids for at least 2 weeks prior to randomization and no evidence of progression or hemorrhage after treatment completed at least 1 month prior to randomization, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose of anticonvulsants is allowed). Treatment for CNS metastases may include whole brain radiotherapy, radiosurgery (eg, RS, gamma knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Participants with CNS metastases treated by neurosurgical resection or brain biopsy performed within 1 month prior to randomization are not eligible. Baseline imaging of the brain is required within 28 days prior to randomization.

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

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

d) 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

e) Any tumor invading the SVC or other major blood vessels

f) Any tumor invading the GI tract or any evidence of endotracheal or endobronchial tumor within 30 days prior to randomization

g) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally (sites in Germany, see Appendix 12).

h) Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis, aortic aneurysm, aortic dissection) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results

i) History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel obstruction, or gastric outlet obstruction within the past 6 months prior to randomization

j) Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of cabozantinib or sunitinib (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection)

k) Serious, non-healing wound or ulcer within 30 days prior to randomization

l) Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 3 months prior to randomization

m) Uncontrolled adrenal insufficiency

n) History of cerebrovascular accident (CVA) including transient ischemic attack within the past 6 months prior to randomization

o) History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within past 6 months prior to randomization unless stable, asymptomatic, and treated with low molecular weight heparin (LMWH) for at least 3 weeks prior to randomization

p) Any unstable cardiac arrhythmia within 6 months prior to randomization

q) Prolongation of the Fridericia corrected QT (QTcF) interval defined as > 450 msec for males and > 470 msec for females, where QTcF = QT / $3\sqrt{RR}$ with triplicate measurements

r) Poorly controlled hypertension (defined as systolic blood pressure (SBP) of > 150 mmHg or diastolic blood pressure (DBP) of > 90 mmHg), despite antihypertensive therapy

s) History of any of the following cardiovascular conditions within 6 months of randomization: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure (CHF), as defined by the New York Heart Association (NYHA)

t) Any radiologic or clinical evidence of pancreatitis within 30 days prior to randomization

u) Inability to swallow oral medications

[redacted]

3) Physical and Laboratory Test Findings

a) Ejection fraction ≤ 50% on screening echocardiogram or MUGA

b) WBC < 2000/μL

c) Neutrophils < 1500/μL

d) Platelets < 100 x 10^3/μL

e) Hemoglobin < 9.0 g/dL (support with transfusion is acceptable)

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

g) AST/ALT > 3.0 x ULN

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

i) Urine protein/creatinine ratio (UPCR) > 1.5, unless 24-hour urine protein is ≤ 1.5 g

j) INR > 1.5

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

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) No history of severe hypersensitivity to a monoclonal antibody

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances, and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.)

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

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

For participants in Arms A (and Arm B participants enrolled prior to Revised Protocol 01), cabozantinib should not be taken with grapefruit/grapefruit juice or Seville oranges.

For participants in Arm C, sunitinib should not be taken with grapefruit/grapefruit juice.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

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

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

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

7 TREATMENT

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

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

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

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

Table 7-1: Study treatments for CA2099ER

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection*	100 mg (10 mg/mL)	IP	Open Label	Vial (multiple vials per carton)	Store at 2° - 8 °C. Protect from light and freezing
Ipilimumab Solution for Injection (see Note)	200 mg (5mg/mL)	IP	Open Label	Vial (multiple vials per carton)	Store at 2° - 8 °C. Protect from light and freezing
Cabozantinib Tablet	20 mg	IP	Open Label	Tablets in a bottle	Refer to storage conditions on container label
Sunitinib Malate Capsule**	12.5 mg	IP	Open Label	Capsules in various packaging configurations	Refer to storage conditions on container label/package insert

*May be labeled as "BMS-936558-01" or "Nivolumab"

** Sunitinib may be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow and agreed to by BMS.

Note: Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinically planned events, per protocol

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

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1 and the dosing scheduled by cycle is presented in Table 7.1-2.

Table 7.1-1: Selection and Timing of Dose

Arm	Study Treatment	Dosage level(s) and Formulation	Frequency of Administration	Route of Administration
A (Doublet)	Nivolumab	240 mg IV	Every 2 weeks	IV
	Cabozantinib	40 mg (20 mg tablets)	Once daily (QD)	PO
B (Triplet) See Note	Nivolumab	3 mg/kg IV for 4 doses then 240 mg IV	Every 3 weeks (Q3W) for 4 doses then every 2 weeks (Q2W)	IV
	Ipilimumab	1 mg/kg IV for 4 doses	Every 3 weeks (Q3W) for 4 doses	IV
	Cabozantinib	40 mg (20 mg tablets)	Once daily (QD)	PO
C	Sunitinib	50 mg (12.5 mg capsules)	A 6 week cycle, consisting of once daily (QD) regimen for 4 weeks followed by no treatment for 2 weeks.	PO

Abbreviations: IV=intravenous; PO= by mouth.

Note: Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinically planned events, per protocol

Table 7.1-2: Dosing Schedule for CA2099ER

Arm	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 and subsequent cycles
Arm A Nivolumab + Cabozantinib (each cycle = 2 weeks)	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD
Arm B Nivolumab + Ipilimumab + Cabozantinib (see Note) (Cycle 1 to 4 = 3 weeks, Cycle 5 and subsequent cyces = 2 weeks)	Nivolumab 3 mg/kg IV on Day 1 + Ipilimumab 1 mg/kg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 3 mg/kg IV on Day 1 + Ipilimumab 1 mg/kg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 3 mg/kg IV on Day 1 + Ipilimumab 1 mg/kg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 3 mg/kg IV on Day 1 + Ipilimumab 1 mg/kg IV on Day 1 + Cabozantinib 40 mg PO QD	Nivolumab 240 mg IV on Day 1 + Cabozantinib 40 mg PO QD

Table 7.1-2: Dosing Schedule for CA2099ER

Arm	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 and subsequent cycles
Arm C Sunitinib (each cycle = 6 weeks, treatment for 4 weeks then 2 weeks off each cycle)	Sunitinib 50 mg PO QD x 4 weeks	Sunitinib 50 mg PO QD x 4 weeks	Sunitinib 50 mg PO QD x 4 weeks	Sunitinib 50 mg PO QD x 4 weeks	Sunitinib 50 mg PO QD x 4 weeks

Abbreviations: IV=intravenous; PO= by mouth; QD= once daily

Note: Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinically planned events, per protocol

Participants should begin study treatment within 3 days (72 hours) of randomization.

For **Arm A**, participants should receive nivolumab at a dose of 240 mg as an approximately 30 minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment (from the first dose on Cycle 1), or the end of the study, whichever occurs first. The first cabozantinib dose should be given in the evening on Day 1, Cycle 1 (after the Cycle 1 nivolumab dose).

For **Arm B (Note: only applicable to participants who randomized to Arm B prior to** Revised Protocol 01**)**, when nivolumab and ipilimumab are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion (approximately 30 minutes) must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug (approximately 30 minutes infusion) and will start after the infusion line has been flushed, filters changed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be at least 30 minutes (from the end of the nivolumab infusion to the start of the ipilimumab infusion). The first cabozantinib dose should be given in the evening on Day 1, Cycle 1 (after the Cycle 1 nivolumab and ipilimumab doses).

Starting with Cycle 5 in Arm B, participants should receive nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment (from the first dose on Cycle 1), or the end of the study, whichever occurs first.

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

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Participants may be dosed with nivolumab no less than 12 days from the previous dose during q2w cycles.

Participants may be dosed with nivolumab and ipilimumab no less than 19 days from the previous dose during q3w cycles (ie, Cycles 1-4 in Arm B). Participants in Arm B may be dosed with the first nivolumab maintenance dose (Cycle 5) no less than 19 days from the previous nivolumab and ipilimumab doses. Premedications are not recommended for the first dose of nivolumab or ipilimumab.

Participants should be carefully monitored for infusion reactions during nivolumab and/or ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. The only exception is Cycle 4 in Arm B, which may be skipped (omitted) only for the reasons specified in Section 7.4.3.1and Section 8.1.1 below.

7.1.1 Nivolumab

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Please refer to the Investigational Brochure/pharmacy manual for further details regarding storage, preparation and administration. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 Ipilimumab (Participants Randomized to Arm B Prior to Revised Protocol 01)

For details regarding ipilimumab storage, preparation, and administration, please refer to the instructions in the ipilimumab IB and/or pharmacy manual.

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

Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

7.1.3 Cabozantinib

Cabozantinib is taken orally on an empty stomach, preferably at bed time. Participants should fast (with the exception of water) for at least 2 hours before until 1 hour after each dose of cabozantinib. Cabozantinib tablets should not be crushed or chewed. Cabozantinib should not be taken with grapefruit/grapefruit juice or Seville oranges. Missed doses of cabozantinib should not be taken within 12 hours of the next dose.

Dispense cabozantinib tablets in their original containers.

7.1.4 Sunitinib

Sunitinib is taken orally without regard to meals. Participants are to avoid grapefruit/grapefruit juice while on treatment with sunitinib.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

Once enrolled in IRT, enrolled participants that have met all eligibility criteria, including determination of PD-L1 expression in the tumor sample submitted to and evaluated by the central laboratory, will be ready to be randomized through the IRT prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required.

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

7.3 Blinding

Not applicable as this is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an Interactive Response Technology (IRT).

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

BICR will remain blinded to treatment assignment.

7.4 Dosage Modification

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

In Arm A and Arm B, the assessment of causality for any AE should be performed independently for each study drug in the combination regimen.

In the doublet treatment arm (Arm A), cabozantinib and nivolumab will be administered at Cycle 1. After Cycle 1, modifications in cabozantinib dosing (delay, reduction/escalation, and discontinuation) may occur as outlined in Section 7.4.1, Section 7.4.2, and Section 8. After Cycle 1, nivolumab may be modified as outlined in Section 7.4.1, Section 7.4.2, and Section 8.

In the triplet treatment arm (Arm B), cabozantinib, nivolumab, and ipilimumab will be administered at Cycle 1. After Cycle 1, modifications in cabozantinib dosing (delay, reduction/escalation, and discontinuation) may occur as outlined in Section 7.4.1, Section 7.4.2, and Section 8. After Cycle 1, nivolumab or ipilimumab may be modified as outlined in Section 7.4.1, Section 7.4.2, and Section 8.

In Arm C, sunitinib will be administered at Cycle 1. After Cycle 1, modifications in sunitinib dosing (delay, reduction/escalation, and discontinuation) may occur as outlined in Section 7.4.1, Section 7.4.2, and Section 8.

7.4.1 Dose Delay Criteria

Dose delay criteria for management of adverse events during nivolumab, ipilimumab, cabozantinib, or sunitinib treatment are outlined in this section.

Dosing of nivolumab (in Arm A) or nivolumab and ipilimumab (in Arm B) may be delayed without delay of cabozantinib dosing if toxicity is felt to be related to only nivolumab (Arm A) or nivolumab and ipilimumab (Arm B) and not related to cabozantinib. Conversely, dosing of cabozantinib may be delayed without delay of nivolumab dosing (in Arm A) or nivolumab and ipilimumab dosing (in Arm B) if toxicity is felt to be related to only cabozantinib and not related to nivolumab (Arm A) or nivolumab and ipilimumab (Arm B). However, if toxicity is considered related to all study drugs or if the investigator is unable to determine which study drug is the cause of the AE, then all study drugs in the combination should be delayed.

Participants who require dose delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met (see Section 7.4.3).

7.4.1.1 Dose Delay Criteria for Nivolumab and Ipilimumab

In Arm A, nivolumab administration should be delayed, and in Arm B, both nivolumab and ipilimumab administration should be delayed, for any of the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require dose delay
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
  - Grade ≥ 3 AST, ALT or total bilirubin will require dose discontinuation (see section 8.1.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

During Cycles 1-4 in Arm B, both nivolumab and ipilimumab must be delayed at the same time.

Immuno-oncology agents, such as nivolumab and ipilimumab, are associated with AEs that differ in severity and duration than AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary

- Hepatic
- Endocrinopathy
- Skin
- Neurological

The management algorithms recommended for use in CA2099ER are included in Appendix 5.

7.4.1.2 Dose Delay Criteria for Cabozantinib

Cabozantinib dosing should be delayed for the following:

- Urine protein/creatinine ratio (UPCR) > 2.0 *or* urine dipstick protein ≥ 3+ *or* urine protein > 2.0 g / 24 hours. Obtain 24 hour urine protein prior to next dosing visit.
- Grade 3 prolonged QTc interval (ie, QTcF interval > 500 msec on at least 2 out of 3 separate ECGs performed at least 3 minutes apart)
- Any Grade 2 or 3 drug-related venous thrombosis requiring anticoagulation, with the following exception:
  - Any recurrent or worsening venous thromboembolic event after restarting cabozantinib will require discontinuation
- Any other Grade 2 drug-related adverse event or grade 2 drug-related laboratory abnormality (e.g., AST, ALT, total bilirubin) that persists for more than 1 week or worsens despite supportive care management, with the following exception:
  - Any Grade 2 drug-related hemorrhage requires dose delay
  - Grade ≥ 2 arterial thromboembolic events, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, require discontinuation
- Sustained Grade 3 drug-related hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg). NOTE: Stopping or reducing the dose of cabozantinib is expected to cause a decrease in BP. The treating physician should monitor the participant for hypotension and adjust the number and dose of antihypertensive medications accordingly.
- Any other Grade 3 drug-related adverse event or laboratory abnormality, with the following exceptions:
  - Grade ≥ 3 drug-related hemorrhage requires discontinuation (Section 8.1.2).
  - Drug-related AST or ALT > 8 x ULN requires discontinuation (Section 8.1.2).
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN, consistent with potential drug-induced liver injury (see Section 9.2.7), requires discontinuation (Section 8.1.2)
  - Grade 3 drug-related amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require dose delay. In such cases, more frequent monitoring (eg, weekly) of amylase and lipase is recommended. If amylase or lipase worsen to Grade 4 severity or the participant develops symptoms or clinical manifestations of pancreatitis, dosing should be delayed.
- Grade 4 drug-related amylase or lipase abnormalities require dose delay. Participants should be monitored for development of symptoms or clinical manifestations of pancreatitis.
- Grade 4 drug-related electrolyte abnormalities require dose delay. Electrolyte correction with supplementation/appropriate management should be promptly initiated.

- Grade 4 drug-related neutropenia, lymphopenia, leukopenia, anemia, or thrombocytopenia
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying cabozantinib dosing
- For participants scheduled for major surgery, including dental surgery which may impact bone healing, cabozantinib dosing should be delayed at least 28 days prior to scheduled surgery. The treating physician should use clinical judgment with regard to the risks and benefits of the planned surgical procedure if it is not possible to delay cabozantinib dosing for 28 days prior to the procedure. A delay of cabozantinib dosing of 5 to 7 days is recommended for healing for minor surgery.

As a general approach, all AEs related to cabozantinib should be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium, and phosphorus should be kept above the lower limits of the laboratory normal values. Please refer to the cabozantinib IB, Appendix 10, and Appendix 11 for additional information regarding dose modifications and AE management.[21]

7.4.1.3 Dose Delay Criteria for Sunitinib

Sunitinib dose delays should be based on instructions in the approved product label and should be considered for any severe or intolerable drug-related adverse events.

Within a cycle, missed doses of sunitinib should be skipped. Participants should never be dosed during the 2-week off period of each 6-week cycle, even if treatment delays occurred earlier in the cycle and therapy is ready to be resumed. If treatment is delayed past the end of the 6-week cycle, the start of the next cycle should be delayed until treatment with sunitinib resumes.

Prior to resuming therapy after a dose delay, refer to Section 7.4.2 for dose reduction recommendations and Section 8 for discontinuation criteria.

For this protocol, sunitinib dosing should be delayed for any of the following:

- Urine protein/creatinine ratio (UPCR) ≥ 2.0 *or* urine dipstick protein ≥ 3+ *or* urine protein ≥ 2.0 g / 24 hours. Obtain 24 hour urine protein prior to next dosing visit.
- Grade 3 prolonged QTc interval (ie, QTcF interval > 500 msec on at least 2 out of 3 separate ECGs performed at least 3 minutes apart)
- Any Grade 2 or 3 drug-related venous thrombosis requiring anticoagulation, with the following exception:
  - Any recurrent or worsening venous thromboembolic event after restarting sunitinib will require discontinuation
- Any other Grade 2 drug-related adverse event that persists or worsens despite supportive care management, with the following exception:
  - Any Grade 2 drug-related hemorrhage requires dose delay
  - Grade ≥ 2 arterial thromboembolic events, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, require discontinuation
- Grade 3 drug-related hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg). NOTE: Stopping or reducing the dose of sunitinib is expected to cause a decrease in BP. The

treating physician should monitor the participant for hypotension and adjust the number and dose of antihypertensive medications accordingly.

- Any other Grade 3 drug-related adverse event or laboratory abnormality, with the following exceptions:
  - Grade ≥ 3 drug-related hemorrhage requires discontinuation (Section 8.1.2).
  - Drug-related AST or ALT > 8 x ULN requires discontinuation (Section 8.1.2).
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN, consistent with potential drug-induced liver injury (see Section 9.2.7), requires discontinuation (Section 8.1.2)
  - Grade 3 drug-related amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require dose delay. In such cases, more frequent monitoring (eg, weekly) of amylase and lipase is recommended. If amylase or lipase worsen to Grade 4 severity or the participant develops symptoms or clinical manifestations of pancreatitis, dosing should be delayed.
- Grade 4 drug-related amylase or lipase abnormalities require dose delay. Participants should be monitored for development of symptoms or clinical manifestations of pancreatitis.
- Grade 4 drug-related electrolyte abnormalities require dose delay. Electrolyte correction with supplementation/appropriate management should be promptly initiated.
- Grade 4 drug-related neutropenia, lymphopenia, leukopenia, anemia, or thrombocytopenia
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying sunitinib dosing
- For participants scheduled for major surgery, including dental surgery which may impact bone healing, sunitinib dosing should be delayed at least 28 days prior to scheduled surgery. The treating physician should use clinical judgment with regard to the risks and benefits of the planned surgical procedure if it is not possible to delay sunitinib dosing for 28 days prior to the procedure. A delay of sunitinib dosing of 5 to 7 days is recommended for healing for minor surgery.

As a general approach, all AEs related to sunitinib should be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium, and phosphorus should be kept above the lower limits of the laboratory normal values. Please refer to the sunitinib approved product label and Appendix 10 for additional information regarding AE monitoring and management.

7.4.2 Dose Reductions and Escalations

Dose reductions are permitted for cabozantinib and sunitinib but not for nivolumab and ipilimumab (see Table 7.4.2-1).

Table 7.4.2-1: Dose Level Modifications Table

Dose Level	**Cabozantinib (tablet dose expression)**	**Sunitinib (capsule dose expression)**	**Nivolumab (IV)**	**Ipilimumab (IV)**	**Nivolumab (IV)**
0 (starting dose)	40 mg daily	50 mg daily	3mg/kg	1 mg/kg	240 mg

Table 7.4.2-1: Dose Level Modifications Table

Dose Level	Cabozantinib (tablet dose expression)	Sunitinib (capsule dose expression)	Nivolumab (IV)	Ipilimumab (IV)	Nivolumab (IV)
-1	20 mg daily	37.5 mg daily	-	-	-
-2	20 mg every other day	25 mg daily	-	-	-

7.4.2.1 Dose Reduction and Escalation for Nivolumab and Ipilimumab

No dose reductions or dose escalations of nivolumab or ipilimumab are allowed.

7.4.2.2 Dose Reduction and Escalation for Cabozantinib

Dose reductions and dose escalations for adverse event management are allowed for cabozantinib (Table 7.4.2-1). Cabozantinib doses will not be re-escalated once reduced, unless a concomitant strong CYP3A4 inducer is started (see below). The only exception is participants who continue on cabozantinib alone after discontinuation of nivolumab alone (Arm A) or discontinuation of both nivolumab and ipilimumab (Arm B) who may re-escalate one dose level if the prior dose reduction was due to a toxicity felt by the investigator to have been mainly related to nivolumab and/or ipilimumab.

After toxicity requiring a dose delay has improved and meets the criteria to resume dosing (Section 7.4.3.2), participants who were receiving cabozantinib 40 mg daily prior to the delay will resume cabozantinib at 20 mg daily. Participants who were receiving cabozantinib 20 mg daily prior to the delay and require another dose delay will resume cabozantinib at 20 mg every other day. If more than 2 dose reductions are necessary (ie, reduction to less than 20 mg every other day), cabozantinib must be permanently discontinued (Section 8.1.2).

Participants who required a dose delay due to Grade 3 hypertension, which improved with antihypertensive medications, or any Grade 2 or 3 drug-related adverse event or asymptomatic laboratory abnormality that improved to Grade ≤ 1 within 7 days with supportive medical care may resume cabozantinib at the same dose or a reduced dose, at the discretion of the investigator.

Participants with asymptomatic Grade 2 drug-related AST, ALT or total bilirubin elevation, or Grade 3 drug-related lipase or amylase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis may reduce cabozantinib by one dose level, without delaying dosing, at the discretion of the investigator. See also section 7.4.1.2.

In Participants Who Start Taking a Concomitant Strong CYP3A4 Inhibitor: Reduce the daily cabozantinib dose by 20 mg (for example, from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor (see Prescribing Information for cabozantinib).

7.4.2.3 Dose Reduction and Escalation for Sunitinib

Sunitinib Dose Reductions are permitted as per the approved product label for safety reasons or when a concomitant strong CYP3A4 inhibitor is needed (Appendix 9). Selection of an alternative

concomitant medication with minimal or no enzyme inhibition potential is recommended whenever possible.

After toxicity requiring a dose delay has improved and meets the criteria to resume dosing (Section 7.4.3.3), participants should resume sunitinib at one dose level reduction. Dose reductions should occur in 12.5 mg decrements. No more than 2 dose reductions are allowed. If more than 2 dose reductions are necessary (ie, reduction to less than 25 mg daily), the participant must be permanently discontinued (Section 8.1.3).

Participants who required a dose delay due to Grade 3 hypertension, which improved with antihypertensive medications, or any Grade 2 or 3 drug-related adverse event or asymptomatic laboratory abnormality that improved to Grade ≤ 1 within 7 days with supportive medical care may resume sunitinib at the same dose or a reduced dose, at the discretion of the investigator.

At the time a dose reduction is considered, also refer to Section 7.4.2.3 for dose delay recommendations and Section 8.1.3 for discontinuation criteria.

Sunitinib Dose Escalations are permitted as per the approved product label when a concomitant CYP3A4 inducer is needed (Appendix 9). Selection of an alternative concomitant medication with minimal or no enzyme induction potential is recommended whenever possible.

7.4.3 Criteria to Resume Treatment

7.4.3.1 Criteria to Resume Nivolumab and Ipilimumab Treatment

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

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, has been completed.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor or designee.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If treatment is delayed > 6 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 8.1.1.

For Arm B participants who delay nivolumab and ipilimumab dosing after Cycle 1 or 2, both nivolumab and ipilimumab must be resumed on the same day when the criteria to resume treatment are met.

For Arm B participants who delay nivolumab and ipilimumab dosing after Cycle 3 due to any drug-related AE meeting dose delay criteria that does not resolve within 14 days or requires treatment with systemic corticosteroids, it is acceptable to omit Cycle 4 if the investigator feels that ipilimumab was the main cause of the toxicity requiring dose delay. In this situation, when the participant meets criteria to resume nivolumab, the participant may proceed to Cycle 5 and begin nivolumab monotherapy maintenance.

7.4.3.2 Criteria to Resume Cabozantinib Treatment

Participants may resume treatment with cabozantinib when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume dosing in the presence of Grade 2 fatigue
- Participants who delayed dosing due to prolonged QTcF may resume dosing at one reduced dose level once QTcF returns to ≤ 500 msec
- Participants who delayed dosing due to UPCR > 2.0 or urine dipstick protein ≥ 3+ or urine protein > 2.0 g / 24 may resume dosing at one dose level reduction when UPCR is ≤ 2.0 or 24 hour urine protein ≤ 2.0 g /24
- Participants who delayed dosing due to Grade 3 hypertension may resume dosing at the same dose or at one dose level reduction, at the discretion of the investigator, when hypertension has improved to Grade ≤ 2
- Participants who delayed dosing due to Grade 4 lipase or amylase abnormalities may resume dosing upon resolution to Grade ≤ 2
- Participants who delayed dosing due to major surgery should not resume cabozantinib until complete wound healing has taken place. Following cabozantinib resumption, participants should be monitored for wound dehiscence, wound infections, and other signs of impaired wound healing.
- Participants who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator.
- Participants who delayed dosing due to ≤ Grade 2 hemorrhage may resume dosing if bleeding is under control (recovered to at least Grade 1 level) and has a low risk of recurrence
- If treatment is delayed > 6 weeks for any reason, the participant must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the BMS Medical Monitor or designee.

7.4.3.3 Criteria to Resume Sunitinib Treatment

Within a cycle, missed doses of sunitinib should be skipped and not replaced. Participants should never be dosed during the 2-week off period of each 6-week cycle, even if treatment delays occurred earlier in the cycle and therapy is ready to be resumed. If treatment is delayed past the end of the 6-week cycle, the start of the next cycle should be delayed until treatment with sunitinib resumes.

Participants may resume treatment with sunitinib when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume dosing in the presence of Grade 2 fatigue
- Participants who delayed dosing due to prolonged QTcF may resume dosing at one reduced dose level once QTcF returns to ≤ 500 msec
- Participants who delayed dosing due to UPCR ≥ 2.0 or urine dipstick protein ≥ 3+ may resume dosing at one dose level reduction when 24 hour urine protein < 2.0 g
- Participants who delayed dosing due to Grade 3 hypertension may resume dosing at the same dose or at one dose level reduction, at the discretion of the investigator, when hypertension has improved to Grade ≤ 2
- Participants who delayed dosing due to Grade 4 lipase or amylase abnormalities may resume dosing upon resolution to Grade ≤ 2
- Participants who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator.
- Participants who delayed dosing due to ≤ Grade 2 hemorrhage may resume dosing if bleeding is under control (recovered to at least Grade 1 level) and has a low risk of recurrence
- If treatment is delayed > 6 weeks for any reason, the participant must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the BMS Medical Monitor or designee.

7.4.4 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Regardless of whether or not the event is attributed to the study drugs, all Grade 3 or 4 infusion reactions should be reported within 24 hours to the study BMS Medical Monitor or designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) guidelines.

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

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

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

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

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study dug will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

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

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

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to

study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

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

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

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

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability (including review of dosing diary cards, as applicable). Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

[redacted]

[redacted]

7.8 Treatment After the End of the Study

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

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Criteria listed in 8.1.1
- Disease progression of RCC or occurrence of a secondary malignancy which requires systemic therapy for treatment

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

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

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

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

8.1.1 Nivolumab and Ipilimumab Dose Discontinuation (Arms A and B)

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

The assessment for discontinuation of nivolumab, ipilimumab, and cabozantinib should be made separately for each study drug. Although there is overlap among the discontinuation criteria, if

discontinuation criteria are met for one study drug but not the other(s), it may be acceptable to continue treatment with the study drug(s) that are not felt to be related the toxicity, as specified below. If the investigator considers the toxicity to be related to all study drugs or is unable to determine which of the study drug(s) in Arm A or Arm B are the cause of toxicity, then all study drugs in the treatment regimen should be discontinued, and the recommendations for management of toxicity related to all study drugs should be promptly initiated.

Nivolumab and/or ipilimumab treatment should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation. NOTE: The diagnosis of colitis should be supported by findings on colonoscopy whenever possible.
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

        * In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase

  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor or designee.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor or designee.

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

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

Participants in Arm B who meet any of the discontinuation criteria above prior to Cycle 3 must discontinue both nivolumab and ipilimumab and may not receive nivolumab monotherapy maintenance.

Participants in Arm B who meet any of the discontinuation criteria above after Cycle 3 or Cycle 4 may be able to proceed to Cycle 5 (skipping Cycle 4 if needed) to begin nivolumab monotherapy maintenance if the toxicity is felt to be related mainly to ipilimumab, only after discussion with and approval by the BMS Medical Monitor or designee.

8.1.2 Cabozantinib Dose Discontinuation

Permanently discontinue cabozantinib for participants with any of the following:

- Any requirement for more than 2 cabozantinib dose reductions (ie, reduction to less than 20 mg every other day)
- Any Grade ≥ 2 drug-related arterial thromboembolic events, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia
- Any Grade ≥ 3 drug-related hemorrhage
- Grade 4 hypertension or persistent Grade 3 hypertension despite optimal medical management and cabozantinib dose reduction
- Drug-related reversible posterior leukoencephalopathy syndrome

- Development of drug-related fistula or GI perforation
- Drug-related nephrotic syndrome
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 8 x ULN.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin >2 x ULN, consistent with potential drug-induced liver injury (see Section 9.2.7).
- Any Grade 4 drug-related adverse event or laboratory abnormality, with the following exceptions:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 4 electrolyte abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks unless the BMS Medical Monitor or designee is consulted and agrees with the rationale for resuming therapy after a delay > 6 weeks. Note that tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued cabozantinib dosing.

8.1.3 Sunitinib Dose Discontinuation

Treatment with sunitinib should be permanently discontinued for any of the following:

- Any requirement for more than 2 sunitinib dose reductions (ie, reduction to less than 25 mg daily)
- Any Grade drug-related arterial thrombosis.
- Grade 4 drug-related hemorrhage or recurrent Grade 3 drug-related hemorrhage after dose reduction.
- Grade 4 drug-related symptomatic venous thrombosis.
- Grade 4 drug-related cardiac toxicity.
- Grade 4 hypertension or persistent Grade 3 hypertension despite optimal medical management and sunitinib dose reduction
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 8 x ULN.
  - Concurrent AST or ALT > 3 x ULN and total bilirubin >2 x ULN, consistent with potential drug-induced liver injury (see Section 9.2.7).
- Any other Grade 4 drug-related adverse event or laboratory abnormality, with the following exceptions:

  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 4 electrolyte abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks unless the BMS Medical Monitor or designee is consulted and agrees with the rationale for resuming therapy after a delay > 6 weeks. Note that tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued sunitinib dosing.

8.1.4 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy or anti-angiogenic therapy may derive clinical benefit despite initial evidence of PD.[19,51,52]

Participants, regardless of study arm, will be permitted to continue treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, up to a maximum of 24 months from the date of first dose, as long as they meet the following criteria:

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

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities Schedule in Section 2. Treatment may be continued beyond investigator-assessed progression if the investigator confirms that the participant meets the criteria specified in Section 8.1.4.

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

diameters of new measurable lesions compared to the time of initial PD. It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.5 Post-Study Treatment Follow-up

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

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (See Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.

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

9 STUDY ASSESSMENTS AND PROCEDURES

CA2099ER Global Revised Protocol 01

Implementation of CA2099ER Global Revised Protocol 01 stops further randomization into Arm B. Participants previously randomized to Arm B continue with Arm B treatment and continue with Arm B clinical planned events, per protocol.

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately

evaluated to rule out pulmonary toxicity, [redacted]

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

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

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099ER Imaging Manual to be provided by the core lab.

9.1.1 Methods of Measurements

The following imaging assessments should be performed at pre-specified intervals: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease.

- CT scans should be acquired with slice thickness of 5 mm or less with no intervening gap (continuous)
- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other sites of disease may be obtained. MRIs should be acquired with slice thickness of 5 mm or less with no gap (continuous).
- Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.

  Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with FDG-PET/CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST (Appendix 8) measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

9.1.2 Imaging and Clinical Assessment

Images will be submitted to an imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA2099ER Imaging Manual to be provided by the core lab.

Baseline imaging, including CT/MRI of the chest, abdomen, pelvis, and all known sites of disease performed within 28 days prior to randomization, should be submitted to the imaging core lab. Baseline brain MRI (preferred) or CT scan should also be performed within 28 days prior to randomization and submitted to the imaging core lab. Participants who are found to have untreated brain metastases on the baseline brain scan may not be randomized.

9.1.2.1 Investigator Assessment of Progression

The same method of assessment used at Screening should be used for on-study time points. Brain MRI or CT scans during on-study time points and the follow-up phase are only required in participants with a history of CNS metastases prior to randomization or if clinically indicated for new signs or symptoms that suggest new or worsening CNS metastases.

Post-baseline tumor assessments will be performed at the time points described below until progression assessed by the investigator **and** confirmed by BICR, death, or withdrawal from the study, whichever occurs first.

- First tumor assessment post-baseline should be performed at Week 12 (± 7 days) following randomization. Use same imaging method as was used at screening/baseline.
- Subsequent tumor assessments should occur at every 6 weeks until Week 60. Allowable window for assessments is ± 7 days until Week 60. After Week 60, tumor assessments should occur every 12 weeks (± 14 days) until radiographic progression, assessed by the investigator **and** confirmed by the BICR.
- Additional imaging of potential disease sites should be performed whenever disease progression or a secondary malignancy is suspected. In participants with no history of brain lesions prior to randomization, brain MRI or CT on-study treatment should be obtained if clinically indicated. Bone imaging during on-study treatment and follow-up periods should be obtained if clinically indicated.
- Tumor assessments are to continue for all randomized participants according to the protocol schedule until radiographic progression has been assessed by the investigator **and** confirmed by the BICR, regardless of whether study drug dosing is delayed, reduced, or discontinued.

The investigator (in consultation with the local radiologist as needed) will complete tumor assessments using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria on all imaging time points specified in the protocol. Any additional imaging that may demonstrate tumor response or progression, including scans performed at unscheduled time points and/or at an outside institution, should also be collected for the investigator to complete RECIST 1.1 tumor assessments on these images and to submit them for BICR review.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2.2 BICR Assessment of Progression

Sites should submit all scans to a BICR on a rolling basis, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans on a rolling basis and remain blinded to treatment arm and investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be performed. The BICR review will be completed and the results provided to the site within approximately 14 days of receipt of the scans, provided there are no pending imaging queries to the site.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule or sooner if clinically indicated until the BICR confirms progression on a subsequent tumor assessment. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2, until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.

9.1.3 Imaging Restriction and Precautions

Table 9.1.3-1 provides a summary of the alternative methods, acceptable per protocol, in the event of contraindications for use of IV and oral contrast, and or/MRI.

Table 9.1.3-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

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

Table 9.1.3-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

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

Notes:

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

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

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

[redacted]

[redacted]

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3

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

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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

Sections 5.6.1 and 5.6.2 in the Investigator Brochures (IBs) for Nivolumab[28] and Ipilimumab[29] represent the Reference Safety Information (also Appendix K in the IB for cabozantinib[21]) to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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 non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 months (5 half-lives + 30 days) after product administration for WOCBP, 7 months (5 half lives + 90 days) after product administration for male participants with partners who are WOCBP, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

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

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

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

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

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

9.4 Safety

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

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology (CBC)
Hemoglobin
Hematocrit

Total leukocyte count, including differential	
Platelet count	
Prothrombin time (PT)/ International normalized ratio (INR)	
Partial thromboplastin time (PTT)	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (MLR) Creatinine Blood Urea Nitrogen (BUN) Glucose Albumin	Sodium (Na) Potassium (K) Chloride (Cl) Calcium (Ca) Corrected calcium (Screening only) Phosphorus (P) Magnesium (Mg) Amylase Lipase
Urinalysis	
Creatinine Protein Urine protein/creatinine ratio (UPCR)	
Serology	
Serum for hepatitis C antibody, HCV RNA, hepatitis B surface antigen (screening only). HIV, if mandated locally. (Sites in Germany, see Appendix 12)	
Other Analyses	
Thyroid stimulating hormone (TSH) with free thyroxine (fT3) and free triiodothyronine (fT4) (screening only); TSH with reflexive fT3 and fT4 during study and follow up	
Pregnancy test (WOCBP only: screening and during study)	
Follicle stimulating hormone (FSH) (screening only for women under 55 years old to confirm menopause as needed)	

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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will be evaluated in this study as noted in Section 2.

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

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

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of this study accounts for the primary endpoint of progression-free survival (PFS) per BICR in all randomized participants. Assuming a 25% screen failure rate, it is expected that approximately 850 participants will need to be enrolled in order to randomize 638 participants (319 per arm) in a 1:1 ratio. To represent the normal frequency of the favorable risk group in mRCC, the favorable risk participants are capped at approximate 25%; thus, at most 212 favorable risk participants (106 per arm) will be enrolled to randomize 160 favorable risk participants in a 1:1 ratio. The rest of the enrolled participants will provide approximately 478 intermediate/poor risk randomized participants (239 per each arm).

The overall alpha for this study is 0.05 (two-sided). PFS will be evaluated for treatment effect at an alpha of 0.05 (two-sided), with at least 95% power. No interim analysis of PFS is planned. OS will be evaluated for treatment effect at an alpha level of 0.05 (two-sided) with 80% power, accounting for two formal interim analyses to assess efficacy.

Sample Size Justification for Primary PFS Endpoint

The primary endpoint of PFS per BICR of Arm A versus Arm C analysis will be conducted on all randomized participants. The PFS analysis will occur after approximately 9-10 months minimum follow-up on all randomized subjects by which approximately 350 events from Arm A and Arm C are expected. The 350 PFS events provide at least 95% power to detect a HR of 0.68 for PFS of Arm A versus Arm C with a type I error of 0.05 (two-sided). The HR of 0.68 corresponds to a 47% increase in the median PFS, assuming a median PFS of 18.2 months for Arm A and 12.4 months for Arm C. It is projected that an observed HR of 0.811 or less, which corresponds to a 2.89 month or greater improvement in median PFS (12.4 versus 15.3 months), would result in a statistically significant improvement in PFS for the Arm A versus Arm C comparison.

If the formal analysis of PFS among all randomized participants is statistically significant, the formal interim analysis of OS among all randomized participants will be tested, as per hierarchical testing procedure.

Sample Size Computation for Secondary OS Endpoint

The secondary endpoint of OS in all randomized participants specifies the comparison of Arm A versus Arm C. Among all randomized participants, approximately 254 events (ie, deaths) in Arm A and Arm C provides at least 80% power to detect a HR of 0.70 for OS of Arm A and Arm C with an overall type 1 error of 0.05 (two-sided) for each test. The HR of 0.70 corresponds to a 43% increase in the median OS, assuming a median OS of 47.1 months for Arm A and 33 months for Arm C.

Two formal interim analyses of OS are planned for this study. The first interim analysis is planned at the time of final PFS analysis and it is expected to observe 165 OS events (65% of the targeted OS events for final analysis) and the second interim analysis is planned to occur after observing approximately 211 events (83% of targeted OS events needed for final analysis). The stopping boundaries at interim and final analyses will be derived based on the number of deaths using O'Brien and Fleming α spending function. For example, with 165, 211, and 254 observed events in Arm A and Arm C at the first interim, second interim, and final analyses, the respective stopping boundaries would be α=0.011 (two-sided), α=0.025 (two-sided), and α=0.041 (two-sided). If the first interim analysis is performed exactly at 165 deaths, it is projected that an observed HR of 0.673 or less, which corresponds to a 16.0 month or greater improvement in median OS (33 versus 49 months), would result in a statistically significant improvement in OS for the Arm A versus Arm C comparison. At the second interim analysis with 211 deaths, it is projected that an observed HR of 0.734 or less, which corresponds to a 12.0 month or greater improvement in median OS (33 versus 45 months), would result in a statistically significant improvement in OS for the Arm A versus Arm C comparison. At the time of final OS analysis when there are 254 deaths, it is projected that an observed HR of 0.774 or less, which corresponds to a 9.6 month or greater improvement in median OS (33 versus 42.6 months), would result in a statistically significant improvement in OS for the Arm A versus Arm C comparison.

Assuming a constant accrual rate (an average rate of 3 participants/month in the first 4 months, afterwards an average rate of 42 participants/month), the accrual will take approximately 19 months. The final PFS analysis will not occur prior to these conditions being met:

- at least 8 months minimum follow-up on all randomized subjects;
- at least 283 PFS events, which provide at least 90% power to detect a HR of 0.68 for PFS of Arm A versus Arm C; and
- at least 149 OS events, which provide 66% power if the target HR for OS was 0.60. (Note that if the analysis of first interim analysis OS takes place with 149 OS events, the alpha spending for the OS comparison would be 0.007 with a critical HR=0.643.)

This expected PFS analysis will occur at approximately 29 months from FPFV. The second interim and final analyses of OS are expected to occur approximately 34 months and 40 months from FPFV, respectively. Table 10.1-1 summarizes the results of these calculations.

Table 10.1-1: Summary of sample size parameters and schedule of analyses

Primary/Secondary Endpoints	PFS (Primary)	OS (Secondary)[a]
Primary analysis population	All Randomized Participants	
Accrual rate per month for all randomized population	3 participants/month in the first 4 months, afterwards an average rate of 42 participants/month	
Power	95%	80%
Alpha	0.05 2-sided	0.05 2-sided (0.011 at IA1, 0.025 at IA2, 0.041 at FA)
Hypothesized median control vs exp (months)	12.4 vs 18.2	33 vs 47.1
Hypothesized hazard ratio	0.68	0.70
Critical hazard ratio (observed hazard ratio at which a statistically significant difference would be observed) / Difference in median (months) Corresponding to a minimal clinically significant effect size (FA)[b]	0.811 / 2.89	0.774 / 9.6
Critical HR at interim analysis-1(IA1) /effect size	N/A	0.673 / 16.0
Expected number of event for IA1 (percentage of target events)	N/A	165 (65%)
Timing of IA1 from FPFV (months)	N/A	29
Critical HR at interim analysis-2(IA2) /effect size	N/A	0.734 / 12.0
Expected number of event for IA2 (percentage of target events)	N/A	211 (83%)
Timing of IA2 from FPFV (months)	N/A	34
Accrual duration (months)	19	19
Timing of final analysis (FA) from FPFV (months)	29	40
Sample size	638	638

Table 10.1-1: Summary of sample size parameters and schedule of analyses

Primary/Secondary Endpoints	PFS (Primary)	OS (Secondary)[a]
Target number of events (Event Goal)	350	254

[a] OS analyses is participant to significance in hierarchical testing strategy for each pairwise comparison.

[b] The difference in median (months) only applies if the control group median is exactly as hypothesized.

10.2 Populations for Analyses

All analyses will be performed using the treatment arm as randomized (intent to treat), with the exception of dosing and safety, for which the treatment arm as received will be used. For purposes of analysis, the following populations are defined in Table 10.2-1, and all populations for analyses given in this table refer to those participants in Arm A and Arm C. Those participants who randomized to Arm B prior to Revised Protocol 01 will be considered as part of the population of interest for descriptive summary of efficacy and safety analyses.

Table 10.2-1: Populations for Analyses

Population	Description
All Enrolled Participants	All participants who sign informed consent and were registered into the IRT.
All Randomized Participants	All participants who were randomized will be used for the analysis of demography, protocol deviations, baseline characteristics, primary efficacy analysis, secondary efficacy analyses, and outcome research analysis which will be performed for this population.
All Treated Participants	All participants who received at least one dose of any study medication. This is the primary population for exposure and safety analyses.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints. A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

The efficacy analyses will be performed in all randomized participants in Arm A and Arm C. Descriptive summary of efficacy will be provided for participants randomized in Arm B.

Table 10.3.1-1: Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint of this study is to compare PFS per BICR of Arm A (doublet) versus Arm C (single agent), in all randomized participants. PFS is defined as the time between the date of randomization and the first date of the documented progression, or death due to any cause, whichever occurs first. Participants who die without a reported progression (and die without start of subsequent anti-cancer therapy) will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment on or prior to initiation of subsequent anti-cancer therapy. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Participants who started anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery) without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of first subsequent anti-cancer therapy. The primary formal comparisons of PFS will be conducted using a two-sided 0.05 stratified log-rank test for each comparison, with IMDC scores, PD-L1 tumor expression, and region at screening per IRT as stratification factors among all randomized participants. Median PFS will be estimated via the Kaplan-Meier product limit method. Two-sided 95% CI for the median PFS will be computed for each randomized arm. Kaplan-Meier plots of PFS will be presented. Hazard ratios (HR) and corresponding two-sided 95% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of PFS. The totality of PFS results will be presented in a single graphical display that includes Kaplan-Meier curves for all treatment arms, the log-rank p-values for the formal comparisons, the HRs and corresponding CIs, and the median PFS estimates and corresponding CIs. The following supportive analyses of PFS will also be conducted: A stratified multivariate Cox regression model will be used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors. The covariates included in this model will be specified in the statistical analysis plan. PFS using an un-stratified log rank test. The hazard ratio associated with treatment will be presented along with the associated two-sided 95% CIs. PFS accounting for missing tumor assessment prior to PFS event (progression or death). This analysis will be performed only if at least 10% of events have missing prior tumor assessment. It will apply the following restriction to the primary definition: If the elapsed time between the PFS event and the last assessment immediately prior to the event is two or more missed visits (more than 12 weeks - 10 days), the participant's PFS will be censored at his/her last tumor assessment prior to the PFS event.
Secondary	The first secondary endpoint is to compare OS of Arm A versus Arm C in all randomized participants. OS is defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died will be censored at the last known alive date. At the time of the primary endpoint analysis, there will be a first interim analysis of OS. The second interim analysis and the final analysis of OS are planned to occur approximately 34 months and 40 months from FPFV, respectively. OS will be compared between these treatment arms using a two sided, 0.05 level log-rank test (adjusted for interim analyses), stratified using IMDC scores, PD-L1 tumor expression, and region at screening as

Table 10.3.1-1: Efficacy Analyses

Endpoint	Statistical Analysis Methods
	stratification factors among all randomized participants. A similar analysis as in PFS will be conducted for OS. Hazard ratio (HR) and corresponding two-sided 95% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of OS. The second secondary endpoint evaluates ORR per BICR for all randomized participants. ORR is defined as the proportion of randomized participants who achieve a best response of complete response (CR) or partial response (PR) using the RECIST 1.1 criteria. Best overall response. (BOR) is defined as the best response designation recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For participants without document progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Duration of response (DOR) is defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last tumor assessment. Responders who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of first subsequent anti-cancer therapy. TTR is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by BICR. DOR and TTR will be evaluated for responders (CR or PR) only. Tumor assessments are scheduled to be performed at Week 12 following randomization, every 6 weeks for the first 12 months and then every 12 weeks until progression. ORR will be analyzed at the time of the final PFS analysis. ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method within each treatment arms. An estimate of the response rate and an associated exact two-sided 95% CI (Clopper and Pearson) will be presented, by treatment group. Sensitivity analysis based on investigator-determined ORR may also be performed. DOR and TTR will also be evaluated.
[redacted]	[redacted]

10.3.2 Safety Analyses

The safety analyses will be performed in all treated participants in Arm A and Arm C. Participants treated in Arm B will be considered in select safety analyses.

Table 10.3.2-1: Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is related to efficacy and there are no primary safety endpoints.
Secondary	Safety will be analyzed at the time of the primary endpoint analysis. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs, imAEs, and select AEs will be tabulated using the worst grade per NCI CTCAE version 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worse grade per NCI CTCAE version 4.0 criteria.
[redacted]	[redacted]

[redacted]

10.3.4 Interim Analyses

Two interim analyses of OS are planned for this study. The first interim analysis of OS is planned at the time of final PFS analysis and expected after observing 165 deaths (approximately 65% of the targeted OS events) have been observed among all randomized participants in Arm A and Arm C based on above accrual rate and the exponential distribution in each arm. These formal comparisons of OS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets spending function with O'Brien and Fleming type of boundary in EAST version 6. If the first interim analysis is performed exactly at 165 deaths, the boundary in terms of statistical significance for declaring superiority would be 0.011 (HR=0.673 with 16 months improvement in median OS for the Arm A versus Arm C comparison (33 versus 49 months)). The second interim analysis of OS

is expected after observing 211 deaths (approximately 83% of the targeted OS events) have been observed among all randomized participants based on above accrual rate and the exponential distribution in each arm. The boundary for declaring superiority in terms of statistical significance for the second interim analysis after 211 events would be 0.025 (HR=0.734 with 12 months improvement in median OS for the doublet versus sunitinib comparison (33 versus 45 months). The boundary for declaring superiority in terms of statistical significance for the final analysis after 254 events would be 0.041 (HR=0.774 with 9.6 months improvement in median OS for the Arm A versus Arm C comparison (33 versus 42.6 months). More details are summarized in Table 10.1-1. An independent statistician external to BMS will perform interim analysis in conjunction with a review by a data monitoring committee.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AHA	alpha hydroxy acid
AI	accumulation index
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APC	antigen-presenting cell
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
AXL	member of the TAM (Tyro-3, Axl, Mer) receptor tyrosine kinases (RTK) subfamily
β-HCG	beta-human chorionic gonadotrophin
Bcl-xL	anti-apoptotic member of the B-cell lymphoma 2 (BCL-2) protein family
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb

Term	Definition
BOR	best overall response
BP	blood pressure
BTLA	B and T lymphocyte attenuator
BUN	blood urea nitrogen
C	Celsius
C	cycle
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca, Ca^{++}	calcium
Cavg	average concentration
Cavgss	average concentration at steady state
CBC	complete blood count
CD	cluster of differentiation
CD3, CD8, CD14, CD28	cluster of differentiation 3, 8, 14, 28
CD137	member of the tumor necrosis factor (TNF) receptor family. Alternative names are TNF receptor superfamily member 9 (TNFRSF9), 4-1BB and induced by lymphocyte activation (ILA)
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
Cl, $C1^{-}$	chloride
CLcr	creatinine clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration

Term	Definition
c-MET	tyrosine-protein kinase mesenchymal-epithelial transition (MET) or hepatocyte growth factor receptor, is a protein that in humans is encoded by the MET gene
CMH	Cochran-Mantel-Haenzel
Cmin, CMIN	minimum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated standards of reporting trials
CR	complete response
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CVA	cerebrovascular accident
CYP	cytochrome p-450
D	day
DBP	diastolic blood pressure
D/C	discontinue
DILI	drug induced liver injury
dL	deciliter
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
DVT	deep vein thrombosis
EA	extent of absorption
EC50	half maximal effective concentration

Term	Definition
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
e.g., eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EQ-5D-3L	EuroQoL Group's instrument to measure general health status
ESR	Expedited Safety Report
F	bioavailability
FA	final analysis
FDA	Food and Drug Administration
FDG-PET	fludeoxyglucose- positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescent in-situ hybridization
FKSI-19	Functional Assessment of Cancer Therapy - Kidney Symptom Index
FLT-3	Fms-related tyrosine kinase 3
FSH	follicle stimulating hormone
fT3, fT4	free thyroxine (fT3), free triiodothyronine (fT4)
FU	follow up
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
GI	gastrointestinal
h	hour
HA	health authorities
HBsAg	hepatitis B surface antigen

Term	Definition
HBV	hepatitis B virus
hCG, HCG	human chorionic gonadotropin
HCO_3^-	bicarbonate
HCV	hepatitis C virus
HFS	hand foot syndrome
HIV	Human Immunodeficiency Virus
HR	heart rate, hazard ratio
HrQoL	health-related quality of life
HRT	hormone replacement therapy
ICD	International Classification of Diseases
IC50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICOS	inducible co-stimulator
i.e., ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IFN-alpha	interferon alphas
IgG1	immunoglobulin G1
IHC	Immunohistochemistry
IL	interleukin
IL-2	interleukin-2
IMAEs, imAEs	immune-mediated adverse events
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	international normalized ratio
IP	investigational product
ipi	ipilimumab
iRAEs	immune-related adverse events
IRB	Institutional Review Board

Term	Definition
IRC	independent radiologic review committee
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K, K^+	potassium
kg	kilogram
KIT	platelet-derived growth factor receptors (PDGFRs)
KPS	Karnofsky Performance Status
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LC-MS-MS	liquid chromatography tandem-mass spectrometry
LDH	lactate dehydrogenase
LFT	liver function test
LINAC	linear accelerator
LLN	lower limit of normal
LMWH	low molecular weight heparin
ln	natural logarithm
MDSCs	myeloid-derived suppressor cells
MER	proto-oncogene tyrosine-protein kinase MER is an enzyme that in humans is encoded by the MERTK gene
MET	mesenchymal-epithelial transition factor, a tyrosine kinase receptor
mg	milligram
Mg, Mg^{++}	magnesium
MHC	major histocompatibility complex
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction

Term	Definition
mmHg	millimeters of mercury
mOS	median overall survival
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MS	mass spectrometry
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
mUC	metastatic urothelial carcinoma
MUGA	multigated acquisition scan
mWHO	modified World Health Organization
μg	microgram
N	number of subjects or observations
N/A, NA	not applicable
Na, Na^+	sodium
NaF	Sodium fluoride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaulable
ng	nanogram
NIMP	non-investigational medicinal products
nivo	nivolumab
NK	natural killer
NKG2D	encoded by KLRK1 gene which is located in the NK-gene complex (NKC)
NR	not reached
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival

Term	Definition
P	phosporous
PCR	polyermase chain reaction
PD	progressive disease, disease progression
PD	pharmacodynamics
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W, Q3W	every 2 weeks, every 3 weeks
QC	quality control
QD, qd	quaque die, once daily
qRT-PCR	quantitative real time polyermase chain reaction
QTcF	Fridericia corrected QT
R^2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	proto-oncogene encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor family of extracellular signalling molecules
RNA	ribonucleic acid
ROS1	proto-oncogene tyrosine-protein kinase ROS is an enzyme that in humans is encoded by the ROS1 gene
ROW	rest of the world
RR	respiratory rate

Term	Definition
RS	radiosurgery
RTK	receptor tyrosine kinases
SAE	serious adverse event
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SD	standard deviation, stable disease
SNP	single-nucleotide polymorphism
SOP	Standard Operating Procedures
Subj	subject
SVC	superior vena cava
t	temperature
T	time
TAMs	tumor-assisted macrophages
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
T-HALF	Half life
TID, tid	ter in die, three times a day
TIE-2	tunica interna endothelial cell kinase 2
TIL	tumour-infiltrating lymphocyte,
TKIs	tyrosine kinase inhibitors
Tmax, TMAX	time of maximum observed concentration
Tregs	regulatory T cells
TRKB	tropomyosin receptor kinase B (TrkB), also known as tyrosine receptor kinase B
TSH	thyroid stimulating hormone
TTR	time to response
TYRO3	tyrosine-protein kinase receptor TYRO3 is an enzyme that in humans is encoded by the TYRO3 gene
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
UV	ultraviolet

Term	Definition
VAS	visual analog rating scale
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
wks	weeks
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity
XL184	cabozantinib

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

Sponsor or designee will provide the investigator with an appropriate (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 or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

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

Subjects/participants unable to give their written consent (eg, stroke or subjects/participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an

opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

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

only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

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

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. 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, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT

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

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

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

SCIENTIFIC PUBLICATIONS

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

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

SERIOUS ADVERSE EVENTS

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

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

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

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

EVALUATING AES AND SAES

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

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

Unacceptable as a Sole Method of Contraception
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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

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

Adverse Prognostic Factors
Clinical
KPS < 80% Time from initial diagnosis (including original localized disease if applicable) to treatment < 1 year
Laboratory
Hemoglobin < LLN Corrected calcium > 10 mg/dL Absolute neutrophil count > ULN Platelet count > ULN

Note: The corrected calcium criterion was adapted from to Heng et al, 2009 to account for local laboratories that may not provide an ULN for corrected calcium.

Abbreviations: KPS= Karnofsky Performance Status; 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

APPENDIX 7 PERFORMANCE STATUS SCORES

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

APPENDIX 8 RADIOLOGIC EVALUATION CRITERIA IN SOLID TUMOURS VERSION 1.1 (RECIST CRITERIA 1.1)

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Subjects must have measureable disease to be eligible for this study.

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 1 measurable tumor lesion. When computed tomography (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 nonmeasurable, which are discussed below.

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/magnetic resonance imaging (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 nonmeasurable)
- 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 nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (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

measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are nonmeasurable.

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 nonmeasurable) 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 locoregional therapy are usually not considered measurable, unless there has been demonstrated progression in the lesion. Measurable lesions may be in an irradiated field as long as there is documented progression, and the lesion(s) can be reproducibly measured.

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 30 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 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 examination 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 1 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 nonpathological 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 (e.g., '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 nontarget) 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 1 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 on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 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 nonpathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 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.

- CR: Disappearance of all non-target lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- PD: Unequivocal progression of existing non-target lesions. (Note: The appearance of 1 or more new lesions is also considered progression).
- NonCR/NonPD: Persistence of 1 or more non-target lesion(s).

3.2.1 Special Notes on Assessment of Non-target Lesions

The concept of progression of non-target disease requires additional explanation as discussed below.

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 1 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 1 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 nonmeasurable), 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 will not be used to assess objective tumor responses.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, that is, 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 preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. 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 that 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.

4 RESPONSE CRITERIA

4.1 Time Point 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: Subjects with Target (+/– Non-target) Disease

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

Abbreviations: 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 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.

4.2 Best Overall Response: All Time Points

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 to the date of radiographic progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), 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.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as specified in Table 2.

When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. In this protocol, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks from randomization in order for SD to be the best response.

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

Table 2: Best Overall Response When Confirmation of CR and PR is Required

Overall Response	Overall Response	Best Overall Response
NE	NE	NE

[a] Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

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.

4.2.1 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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 progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded on study), subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery) is initiated, or the participant dies, whichever occurs first.

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery) is initiated, or the participant dies, whichever occurs first.

4.3.2 Duration of Stable Disease

If SD is the best overall response, the duration of SD is measured from the 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), subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery) is initiated, or the participant dies, whichever occurs first..

[redacted]

APPENDIX 10 SUPPORTIVE CARE GUIDELINES FOR THE MANAGEMENT OF HAND FOOT SYNDROME (HFS)

Supportive Care Guidelines for the Management of Hand Foot Syndrome (HFS)

Management of HFS can begin before any symptoms occur. Several prophylactic measures may be taken to prevent or reduce the severity of HFS. Before therapy with begins, a full-body skin exam should be performed, with a special emphasis on hyperkeratotic areas on palms and soles and any deformities. Patients can receive a pedicure, using properly sterilized utensils, to remove any preexisting hyperkeratotic areas or calluses that may predispose them to developing HFS reaction. Patients should be advised to reduce the exposure of their hands and feet to hot water, either through dishwashing or hot baths and showers, because this is believed to exacerbate symptoms, and patients frequently report symptomatic relief with cold water.

Before initiating treatment:

- Check condition of hands and feet
- Suggest a manicure/pedicure, when indicated
- Recommend pumice stone use for callus or 'rough spot' removal

During treatment:

- Avoid pressure points
- Avoid items that rub, pinch, or create friction
- Apply non-urea based skin-hydrating creams liberally
- Keratolytic creams: Use sparingly and only to affected (hyperkeratotic) areas.

Urea-based creams:

- Salicylic acid 6%
- Alpha hydroxy acid (AHA) based creams
- Concentrations of approximately 5-8% provide gentle chemical exfoliation
- Apply liberally two times each day

Topical analgesics like lidocaine 2% should be considered for pain control

Topical corticosteroids like clobetasol 0.05% should be considered for patients with grade 2 or 3 hand-foot skin reaction. Avoid systemic steroids.

Cushions:

- Protect tender areas
- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g., silicon, gel)
- Foot soaks with tepid water and Epsom salts

APPENDIX 11 SUPPORTIVE CARE GUIDELINES FOR THE MANAGEMENT OF DIARRHEA FOR CABOZANTINIB

Participants should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 1.

Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some participants may require concomitant treatment with more than 1 antidiarrheal agent. When therapy with antidiarrheal agent does not control diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good hygiene should be emphasized. Regular examinations of the perianal region should be performed wherever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 1: Guidelines for Management of Treatment-Emergent Diarrhea for Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide daily]) • Dietary modifications (e.g., small lactose-free meals, bananas and rice) • Intake of isotonic fluids 1-1.5 L/day) • Re-assess after 24 hours: - Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval - Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48h, or ≥ Grade 3	• Interrupt study treatment • Ask participant to attend clinic • Rule out infection (e.g., stool sample for culture) - Administer antibiotics as needed, (e.g., if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids 1-1.5L/day orally or IV, as appropriate for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 hour • Diarrhea resolving to baseline bowel habits or Grade ≤ 1: - Consider restarting study treatment at reduced dose • Diarrhea not resolving: - Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum 16 mg loperamide per day - Consider starting second line antidiarrheal or referral to gastroenterologist

APPENDIX 12 COUNTRY SPECIFIC REQUIREMENTS

COUNTRY SPECIFIC REQUIREMENTS

Country Location	Original language	Country-specific language
Germany, Czech Republic, Romania at all sites where it is mandated by local or country regulations	Section 2 Schedule of Activities, Table 2-1, Screening Procedural Outline, Laboratory Tests	Add "HIV" to the list of laboratory tests
Germany, Czech Republic, Romania at all sites where it is mandated by local or country regulations	Section 6.2 Exclusion Criteria, Exclusion criterion 1 g)	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".
Czech Republic	Section 8.1: Discontinuation from Study Treatment	Second paragraph modified to read: "In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy." The following statement is deleted: "If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur."
Czech Republic, Romania	Section 9.4.1: Clinical Safety Laboratory Assessments	Serology section modified to read: Serum for hepatitis C antibody, HCV RNA, hepatitis B surface antigen (screening only). HIV testing must be performed at sites where mandated by local or country regulations, see Appendix 12)

APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

This Revised Protocol 01 applies in all countries, at all sites, to all future participants enrolled in the study, and where applicable, to all participants currently enrolled in the study

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change
Title Page and Synopsis Protocol Title	In the Protocol Title, Arm B wording is deleted.
Synopsis and Section 4 Objectives and Endpoints	Arm B wording is deleted. Objectives and endpoints for intermediate/poor risk groups are deleted [redacted]
Synopsis and Section 5.1 Design	Arm B wording is deleted. Number of Arms is revised from 3 to 2, and treatment allocation to 1:1. Sample size is revised Favorable risk cap is adjusted up to 25% Schematic is revised Impact of Revised Protocol 01 on Arm B patients is clarified
Synopsis, Table 2-3, and Multiple Sections 5.1, 7, 7.1, 7.1.2, 7.4, 8.1.1, 9, 9.5	A paragraph is added to clarify the impact of Revised Protocol 01 on Arm B patients
Procedural Outline Tables 2-2, 2-3 and 2-4	Tumor Tissue row, Notes column - a paragraph is added to clarify procedures associated with Treatment beyond Progression
[redacted]	[redacted]
Section 3.1.1 Research Hypothesis	Arm B wording is deleted.
Section 3.2.1.3 Ipilimumab in Renal Cell Carcinoma	Section deleted as no longer relevant
Section 3.2.1.3 Nivolumab Plus Ipilimumab in Renal Cell Carcinoma	[redacted] (Section numbering is adjusted from 3.2.1.4 to 3.2.1.3, after deletion of prior section 3.2.1.3)

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	[redacted]
Section 3.2.1.4 Cabozantinib Monotherapy in Renal Cell Carcinoma	Paragraph regarding cabozantinib efficacy is updated with ESMO data	
[redacted]	Arm B wording is deleted. [redacted]	
Section 5.1.1 Data Monitoring Committee	Data Monitoring Committee review after 30 patients are treated for 6 weeks, is added.	
Section 5.2 Number of Participants	Sample size is adjusted	
[redacted]	Arm B wording is deleted. Number of Arms is revised from 3 to 2, and treatment allocation to 1:1. Favorable risk cap is adjusted up to 25%	
[redacted]	Arm B wording is deleted. Number of Arms is revised from 3 to 2, and treatment allocation to 1:1.	
[redacted]	[redacted]	
[redacted]	Arm B wording is deleted. [redacted]	
[redacted]	Arm B wording is deleted [redacted]	
[redacted]	Arm B wording is deleted.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change
Dosing Duration for Nivolumab	With this revised protocol, the option for retreatment on study in subjects who progress after completing 2 years of nivolumab treatment will be removed from the protocol.
Synopsis and Section 6.2.1a Exclusion Criteria	Exclusion criteria 6.2.1a revises criteria for CNS metastases that are treated and stable, from at least 3 months to at least 1 month
Section 6.2.1b Exclusion Criteria	Exclusion criteria 6.2.1b adds 'celiac disease' as an example external trigger.
Section 6.2.1o Exclusion Criteria	Exclusion criteria 6.2.1o revises LMWH criteria for DVT and PE, from at least 6 weeks to at least 3 weeks
Section 6.2.2e Exclusion Criteria	Exclusion criteria 6.2.2e is revised to major surgery less than 6 weeks, nephrectomy less than 4 weeks, prior to randomization, provided complete wound healing and no ongoing post-operative complications.
Section 6.2.2g Exclusion Criteria	An exclusion is added regarding botanical preparations
Section 6.2.3f Exclusion Criteria	Exclusion criteria 6.2.3f is clarified
Section 6.2.3i Exclusion Criteria	Exclusion criteria 6.2.3i adjusts UPCR limit to permit UPCR = 1.5, unless 24-hour urine protein is ≤ 1.5 g
Section 7.1 Treatment	Clarification of a sentence revising '...approximately 30 minutes...' to read '...at least 30 minutes...'. For consistency, the phrase 'but may be more or less depending on the situation' is deleted.
Section 7.4.1.2 Dose Delay Criteria for Cabozantinib	Clarifies that Grade 2 drug-related adverse event or laboratory abnormality (e.g., AST, ALT, total bilirubin) that persists for more than 1 week or worsens despite supportive care management, will delay cabozantinib dosing

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change
Section 7.4.1.3 Dose Delay Criteria for Sunitinib	The final paragraph refers the Investigator to the sunitinib label for additional information regarding monitoring of adverse events, in addition to management of adverse events.
Section 7.4.2.2 Dose Reduction and Escalation for Cabozantinib	Participants with asymptomatic Grade 2 drug-related AST, ALT or total bilirubin elevation, or Grade 3 drug-related lipase or amylase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis may reduce cabozantinib by one dose level, without delaying dosing, at the discretion of the investigator.
Section 7.4.3.1 Criteria to Resume Nivolumab and Ipilimumab Treatment	Bullet 4 is deleted: Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
Section 7.4.3.2 Criteria to Resume Cabozantinib Treatment	Addition of a new bullet; Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator.
Section 7.7.1	[redacted]
Section 7.7.2.1	[redacted]s
Section 8.1.1	Addition of myocarditis to Nivolumab and or Ipilimumab discontinuation criteria

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	[redacted]
Section 10 Statistical Considerations	Arm B wording is deleted. Number of Arms is revised from 3 to 2, and treatment allocation to 1:1. The analysis is revised from intermediate/poor risk groups to all risk groups Favorable risk cap is adjusted up to 25% The sample size is adjusted from N=1014 to N=580 randomized. Analysis populations, Efficacy Analysis, Safety Analysis and Interim Analysis are revised accordingly.	
Appendix 2	Deleted bullets describing records maintained by site	
Appendix 4	Add a barrier method of contraception for patients in Arms A and or B.	
Appendix 7	Corrected status definitions of Zubrod-ECOG-WHO scores	
All	Formatting and typographical corrections	