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CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Controlled Phase 3 Study of Cabozantinib in Combination with Nivolumab and Ipilimumab versus Nivolumab and Ipilimumab in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk

PROTOCOL NUMBER:	XL184–313
STUDY TREATMENT:	Cabozantinib in Combination with Nivolumab and Ipilimumab vs Nivolumab and Ipilimumab in Combination with Placebo
IND NUMBER:	140,521
EudraCT NUMBER:	2018-004567-31
SPONSOR:	Exelixis, Inc. 1851 Harbor Bay Parkway Alameda, CA 94502
MEDICAL MONITOR:	PPD
DATE FINAL (Version 0.0):	03 October 2018
DATE AMENDED:	25 February 2019 **AMENDMENT 1.0**
DATE AMENDED:	09 January 2020 **AMENDMENT 2.0**
DATE AMENDED:	16 November 2020 **AMENDMENT 3.0**

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PROTOCOL APPROVAL PAGE

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PROTOCOL ACCEPTANCE FORM

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By my signature below, I hereby state that I have read, and agree to abide by, the instructions, conditions, and restrictions of the protocol or protocol amendment referenced above.

_____

Name of Investigator (print)

_____

Name of Investigator (signature) Date

PROTOCOL SYNOPSIS

TITLE

A Randomized, Double-Blind, Controlled Phase 3 Study of Cabozantinib in Combination with Nivolumab and Ipilimumab versus Nivolumab and Ipilimumab in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk

PROTOCOL NUMBER

XL184-313

CLINICAL PHASE

Phase 3

RATIONALE

Multi-targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) represent two systemic modalities that have been instrumental in the recent advancements of anticancer treatment over the past several years. Both classes of therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types including genitourinary cancers. The success of these therapy types as single agents with distinct mechanisms of action has led to interest in evaluating combinations of TKIs with ICIs in search of further, possibly synergistic, anticancer clinical effects.

Cabozantinib (XL184) is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) known to play important roles in tumor cell proliferation and/or tumor neovascularization including the vascular endothelial growth factor receptor (VEGFR), MET, AXL, and RET. Inactivation of the von Hippel-Lindau (VHL) tumor suppressor protein in clear cell renal cell carcinoma (RCC) results in upregulation of VEGF, MET, and AXL. Increased expression of MET and AXL has been associated with poor prognosis in RCC (Gibney et al 2013, Zhou et al 2016, Ciamporcero et al 2015). In addition, targets of cabozantinib, including TYRO3, MER, and AXL (TAM family kinases), are implicated in promoting suppression of an antitumor immune response. Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment which might present an opportunity for synergistic effects from combination treatment with ICIs independent of tumor programmed death receptor -1 ligand (PD-L1) expression.

Cabozantinib (60 mg, tablets) has been compared with everolimus in patients with advanced RCC who had received prior therapy with at least one VEGFR-TKI in multicenter, randomized, open-label, controlled Phase 3 study (METEOR; Choueiri et al 2015, Choueiri et al 2016). In this trial, 658 subjects were randomized to receive cabozantinib (n = 330) or everolimus (n = 328). After a minimum follow-up of 11 months in the first 375 randomized subjects, the primary endpoint of PFS (by blinded independent radiology committee [BIRC]) was 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm (hazard ratio [HR] 0.58 [95% confidence interval {CI} 0.45, 0.75]; p-value < 0.001). Using Memorial Sloan Kettering Cancer Center (MSKCC) criteria,

subgroup analyses of risk groups demonstrated a progression-free survival (PFS) benefit in subjects with favorable risk (HR 0.54 [95% CI 0.37, 0.79]), intermediate risk (HR 0.56 [95% CI 0.37, 0.84]), and poor risk (HR 0.84 [95% CI 0.46, 1.53]). Objective response rate (ORR) per BIRC was 17% in the cabozantinib arm vs 3% in the everolimus arm (p-value < 0.001). An interim overall survival (OS) analysis at the time of this final PFS analysis demonstrated a trend toward longer OS (HR 0.67, p-value = 0.005, with p-value ≤ 0.0019 required for statistical significance). A subsequent OS analysis, performed after a median follow-up of approximately 19 months in all 658 randomized subjects, demonstrated a significant improvement in OS, with median OS of 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm (HR 0.66 [95% CI 0.53, 0.83]; p-value = 0.00026). Subgroup analyses of OS according to each MSKCC risk group were consistent with the results for the overall population.

Cabozantinib (60 mg, tablets) has also been compared with sunitinib in previously untreated advanced RCC patients in a randomized Phase 2 study (CABOSUN; Choueiri et al [Ann Oncol] 2017, Choueiri et al [Eur J Cancer] 2018). In this trial, subjects were required to have either intermediate or poor risk disease according to International Metastatic RCC Database Consortium (IMDC) criteria and were randomized in a 1:1 ratio to receive either cabozantinib (n = 79) or sunitinib (n = 78). The primary endpoint in this trial was PFS. Compared with sunitinib, cabozantinib treatment significantly increased median PFS per BIRC (8.6 vs 5.3 months) and was associated with a 52% reduction in rate of progression or death (HR = 0.48; 95% CI 0.31, 0.74; two-sided p-value = 0.0008). The ORR per BIRC was 20% (95% CI 12.0, 30.8) for cabozantinib vs 9% (95% CI 3.7, 17.6) for sunitinib. Median OS was 26.6 months for cabozantinib vs 21.2 months for sunitinib (HR = 0.80; 95% CI 0.53, 1.21) (Choueiri et al [Eur J Cancer] 2018). Cabozantinib treatment was associated with OS and PFS benefit in both intermediate and poor IMDC risk categories.

Cabozantinib (60 mg, tablets) is approved in the US for the treatment of patients with advanced RCC and in the EU for the treatment of adult patients with advanced RCC after prior VEGF-targeted therapy or treatment-naïve adult patients with intermediate or poor risk RCC (Cabometyx™ US PI and EMA SmPC). Cabozantinib (60 mg, tablets) is also approved in the US and EU for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (Cabometyx US PI and EMA SmPC), based on the results of a randomized, double-blind, placebo-controlled, multicenter trial showing that treatment with cabozantinib was associated with statistically significant improvements in OS, PFS and ORR. Cabozantinib (140 mg, capsules) is also approved in the United States and in Europe, for the treatment of progressive, metastatic medullary thyroid cancer (MTC; Cometriq™ US PI and EMA SmPC). This was based on the results of a multicenter, randomized, double-blind, controlled Phase 3 study comparing cabozantinib (140 mg, capsules) with placebo in which cabozantinib demonstrated a statistically significant improvement of the primary endpoint of PFS (Elisei et al 2013). The capsule and tablet formulations are not bioequivalent or interchangeable.

Nivolumab is a fully-human monoclonal immunoglobulin G4 (IgG4) kappa antibody specific for human programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Through the inhibition of the interaction of PD-1 with its ligands (PD-L1 and PD-L2), nivolumab has demonstrated the ability to generate increased anti-tumor immune responses and improvements in survival of cancer patients.

Single-agent nivolumab has been approved in multiple cancer types including patients with advanced RCC after prior antiangiogenic therapy in the US and in patients with advanced RCC after prior therapy in Europe (Opdivo™ US PI and EMA SmPC).

Ipilimumab is a fully-human monoclonal IgG1kappa antibody that binds to the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antigen expressed on a subset of human T cells. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA4/B7 interaction. Single-agent ipilimumab is approved in the US and Europe for the treatment of unresectable or metastatic melanoma (Yervoy™ US PI, EMA SmPC).

In a randomized Phase 3 trial (CheckMate 214; Motzer et al 2018), 1096 subjects with previously untreated advanced RCC were randomized to receive nivolumab and ipilimumab (nivo+ipi; n=550) or sunitinib (n=546). The primary endpoints were OS, PFS per BIRC, and ORR per BIRC in the IMDC intermediate- and poor-risk subjects. At a median follow-up of 25.2 months, the 18-month OS rate was 75% (95% CI 70, 78) with nivo+ipi vs 60% (95% CI 55, 65) with sunitinib; the median OS was not reached with nivo+ipi vs 26.0 months with sunitinib (HR = 0.63 [95% CI 0.44, 0.89]; p-value < 0.001; by interpolation median OS for the nivo+ipi arm is estimated to be approximately 41 months). The median PFS by BIRC in the intermediate- and poor-risk population was 11.6 months vs 8.4 months (HR 0.82 [95% CI 0.64, 1.05]; p-value = 0.03). With extended follow-up in intermediate-risk or poor-risk patients, results for all three primary efficacy endpoints now show that nivolumab plus ipilimumab continues to be superior to sunitinib (Motzer et al 2019). The ORR in this population was 42% (9% complete response [CR]) for the nivo+ipi arm vs 27% (1% CR) for the sunitinib arm. The results from this study led to approval in the US and other regions of nivolumab in combination with ipilimumab for patients with intermediate or poor risk, previously untreated advanced RCC (Opdivo US PI/SmPC and Yervoy US PI/SmPC). Based on 4 years of follow-up, the median OS for the active arm (nivolumab plus ipilimumab) in intermediate or poor risk subjects was reported to be 48.1 months (Albiges et al 2020), approximately 7 months longer than originally projected for the control arm in the XL184-313 study.

Cabozantinib has been evaluated in combination with nivolumab (referred to as doublet) and in combination with nivolumab and ipilimumab (referred to as triplet) in an ongoing Phase 1 clinical trial in subjects with various pretreated advanced genitourinary cancers (Apolo et al [Ann Oncol] 2016, Nadal et al 2017, Nadal et al 2018). In the dose escalation stage of the study, no dose limiting toxicities (DLTs) were reported for either the doublet or triplet combination. The recommended Phase 2 dose (RP2D) for the doublet was cabozantinib 40 mg orally once daily (qd) with nivolumab 3 mg/kg administered intravenously (IV) every 2 weeks (q2w) and the RP2D for the triplet was cabozantinib 40 mg qd with nivolumab 3 mg/kg IV q3w and ipilimumab 1 mg/kg IV q3w (maximum 4 doses) followed by nivolumab 3mg/kg IV q2w. Data are available for a total of 78 subjects enrolled in this trial, including 14 subjects with RCC. The ORR for 13 RCC subjects evaluable for response for either the doublet or triplet combination was 54% (7 responders of 13 subjects). The remainder of RCC subjects evaluable for response (6 of 13) had stable disease (SD) reported as their best response to date. The median PFS in these RCC subjects was 18.4 months (95% CI 6.4, 18.4) and the median OS was not reached. Most frequent treatment-related Grade 3 or 4 adverse events (AEs) across all genitourinary cancer indications

and dose levels for the triplet therapy (n=29) included hypertension (10%), diarrhea (10%), fatigue (7%), anorexia (3%), mucositis (3%), proctitis (3%) and thromboembolic events (3%). Two cases of hepatitis (Grade 3 or 4) and one case of immune-related colitis (Grade 3 or 4) were reported for the triplet therapy. Grade 3 or 4 laboratory abnormalities reported in subjects treated with the triplet therapy across all explored dose levels included hypophosphatemia (n=6), increased lipase (n=4), decreased lymphocyte count (n=4), hypokalemia (n=3), alanine aminotransferase (ALT) increased (n=3), aspartate aminotransferase (AST) increased (n=3), hyponatremia (n=2), amylase increased (n=2), hypocalcemia (n=1), and decreased platelet counts (n=1). There were no Grade 5 AEs. Following the encouraging Phase 1 results of the combination of cabozantinib and nivolumab, a randomized Phase 3 trial (CheckMate 9ER, NCT03141177) has been initiated evaluating the efficacy of cabozantinib in combination with nivolumab versus sunitinib in previously untreated advanced or metastatic RCC.

The recently reported results from the CheckMate 9ER study indicated that cabozantinib in combination with nivolumab improved PFS (HR 0.51 [95% CI 0.41, 0.64], $P < 0.0001$; median, 16.6 vs 8.3 mo) and OS (HR 0.60 [98.89% CI 0.40, 0.89]; $P = 0.0010$; medians not reached) versus sunitinib (Choueiri et al 2020) in previously untreated advanced renal cell carcinoma. These results were consistent across all prespecified IMDC risk and PD-L1 subgroups. Furthermore, the ORR (95% CI) was significantly higher with cabozantinib in combination with nivolumab compared to sunitinib (55.7% [50.1-61.2] vs 27.1% [22.4-32.3]; $P < 0.0001$), and 8.0% versus 4.6% of patients achieved complete response. Median duration of response was 20.2 months for patients treated with cabozantinib in combination with nivolumab compared to 11.5 months for patients treated with sunitinib.

In the Phase 3 CheckMate 214 study, the combination of nivolumab with ipilimumab showed efficacy in previously untreated intermediate- and poor-risk RCC subjects (NCT02231749; Motzer et al 2018). However, there was only modest clinical benefit for this therapy in the subgroup of subjects with low PD-L1 (PD-L1 <1%) which accounts for approximately two thirds of this patient population. Patients with low PD-L1 may respond well to VEGF-targeted agents. Therefore, combination of nivolumab and ipilimumab with cabozantinib is attractive because of the potential for improved clinical outcomes for all subjects irrespective of PD-L1 expression (Apolo et al 2014). Further evaluation of cabozantinib in combination with nivolumab and ipilimumab in previously untreated RCC patients of intermediate- and poor-risk is warranted.

The current Phase 3 study evaluates the safety and efficacy of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in combination with placebo in previously untreated subjects with locally advanced or metastatic RCC of intermediate- or poor-risk (as defined by IMDC criteria). Masking (blinding) oral study medication in the experimental and control arm will minimize the potential for bias and help ensure that both study arms are treated and assessed similarly throughout the trial.

OBJECTIVES and ENDPOINTS

The objective of this study is to evaluate the efficacy and safety of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in previously untreated subjects with intermediate- and poor-risk advanced or metastatic RCC.

Primary efficacy endpoint:

- Duration of PFS, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), by Blinded Independent Radiology Committee (BIRC)

Secondary efficacy endpoint:

- Duration of OS

Additional endpoints:

- ORR per RECIST 1.1 by BIRC
- PFS and ORR per RECIST 1.1 by BIRC according to PD-L1 status
- PFS and ORR per RECIST 1.1 as assessed by the Investigator
- Duration of radiographic response as assessed by the Investigator and by BIRC
- Safety through the evaluation of AEs, including immune-related AEs (irAEs), and other safety assessments.
- Pharmacokinetics (PK) of cabozantinib given in combination with nivolumab and ipilimumab
- Immunogenicity of nivolumab and ipilimumab given in combination with cabozantinib
- Correlation of biomarker analyses with clinical outcomes
- Health-related quality of life (HRQoL) as assessed by the EuroQol Health questionnaire instruments (EQ-5D-5L)
- Health care resource utilization

STUDY DESIGN

This is a multicenter, randomized, double-blinded, controlled Phase 3 trial of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in combination with matched placebo.

Approximately 840 eligible subjects with intermediate- or poor-risk advanced or metastatic RCC by IMDC criteria will be randomized in a 1:1 ratio at approximately 180 sites. The study was originally designed to enroll 676 subjects; the sample size was increased to accommodate new, external data about the expected median OS in the control arm (see Section 9.5).

Special accommodations during the global COVID-19 pandemic are described in Appendix K.

Pre-Treatment Period: Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive double-blinded study treatment as follows:

Experimental arm:
Cabozantinib (40 mg oral, once daily [qd]) + nivolumab (3 mg/kg infusion, once every 3 weeks [q3w]) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses,
followed by cabozantinib (40 mg oral qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.

Control arm:
Cabozantinib-matched placebo (oral, qd) + nivolumab (3 mg/kg infusion, q3w) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses,
followed by cabozantinib-matched placebo (oral, qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.

Randomization will be stratified by the following factors established at screening:

- IMDC prognostic score (1-2 risk factors [intermediate] vs 3-6 risk factors [poor])
- Region ([US or Canada or Europe or Australia or New Zealand] vs [Latin America or Asia])

The IMDC risk factors (Heng et al 2009) are the following:

- Karnofsky performance status (KPS) < 80%
- Less than 1 year from initial RCC diagnosis (including original localized disease if applicable) to systemic treatment
- Hemoglobin < lower limit of normal (LLN)
- Corrected calcium > 10 mg/dL
- Absolute neutrophil count (ANC) > upper limit of normal (ULN)
- Platelet count > ULN

Subjects will receive study treatment (see Investigational Regimen below) as long as they continue to experience clinical benefit in the opinion of the Investigator or until there is unacceptable toxicity, the need for subsequent systemic anti-cancer treatment, or any other reasons for treatment discontinuation listed in the protocol. Treatment may continue after radiographic progression per RECIST 1.1 as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks (Section 5.7.6.2).

Crossover between treatment arms will not be allowed.

Transition to Unblinded Treatment: The study may transition to unblinded treatment at the discretion of the Sponsor and upon any necessary discussions with regulatory authorities after analyses of PFS and OS have been performed. If the study is declared futile or the null hypothesis for the primary endpoint of PFS is not rejected (negative study), the study will be unblinded and investigators and subjects will be notified. If the null hypothesis for the primary endpoint of PFS

is rejected (positive study), the study will not be unblinded until the null hypothesis for the secondary endpoint of OS is rejected or the final analysis of OS is performed.

Once the study transitions to unblinded treatment, investigators and subjects will be notified of the randomized treatment assignment to allow for appropriate treatment decisions. Protocol procedures and assessments will continue without change.

Post-Treatment Period: Subjects who discontinue from study treatment (including subjects in the Maintenance Phase [below]) will return to the site for two follow-up visits for safety assessments. The first Post-Treatment Follow-up Visit (FU-1) for safety evaluation is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 (±14) days after the date of the decision to permanently discontinue study treatment.

Radiographic tumor assessments and health-related quality of life (HRQOL) assessments are to continue, regardless of whether study treatment is given, reduced, held or discontinued until a protocol-defined criterion for ending radiographic assessments is met. Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

In addition, subjects are to be contacted every 12 weeks (± 14 days) after the 100-day FU-2 visit to assess survival status and document receipt of systemic non-protocol anti-cancer therapy (NPACT). This will continue until the subject expires or the Sponsor decides to discontinue collection of these data. Further, coinciding with each analysis of OS, sites will be required to determine the survival status for all subjects not known to be deceased as of the data cutoff date for the analysis. This will require additional subject contacts outside the 12-week schedule. Every effort must be made to collect this protocol-specific information unless consent for non-interventional study assessments is withdrawn. Assessments of OS/NPACT are not required in the Maintenance Phase (below).

Study Completion: The study will be considered complete if any of the following criteria apply:

- futility analysis of PFS: the trial has been declared futile by the Sponsor, or
- primary analysis of PFS: null hypothesis is not rejected, or
- primary analysis of PFS: null hypothesis is rejected for PFS and the null hypothesis is rejected for OS (or the final planned analysis for OS has been conducted)

Maintenance Phase/Treatment After Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, and after treatment assignment has been unblinded, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects on active study treatment will continue to receive study treatment until they meet the protocol-required criteria for treatment discontinuation. Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments. The nature and frequency of these assessments during the Maintenance Phase are to be performed per institutional standard of care and guidance from the Sponsor as necessary. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of SAEs; certain AEs (including AESIs [whether serious or not], and AEs leading to dose modifications or treatment discontinuation); and other reportable events (drug-induced liver injury [DILI], pregnancy, and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

The study clinical database will be closed upon initiation of the Maintenance Phase. Important safety information (noted above) collected in the Maintenance Phase will be captured in the

safety database. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

End of Trial: End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

NUMBER OF SUBJECTS

Approximately 840 eligible subjects will be randomized 1:1 to receive cabozantinib in combination with nivolumab and ipilimumab or nivolumab and ipilimumab in combination with placebo (420 per arm).

The study was originally designed to enroll 676 subjects; the sample size was increased to accommodate new, external data about the expected median OS in the control arm (see Section 9.5).

TARGET POPULATION

To be eligible for the study the subject must meet all of the inclusion and none of the exclusion criteria. The Sponsor will not grant exceptions to these eligibility criteria:

Inclusion Criteria

1. Histologically confirmed advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) renal cell carcinoma with a clear-cell component, including subjects who also have a sarcomatoid feature.
2. Intermediate- or poor-risk RCC as defined by IMDC criteria (Section 3.4).
3. Measurable disease per RECIST 1.1 as determined by the Investigator. Measurable disease must be outside the radiation field if radiation therapy was previously administered.
4. Shipment of archival tumor tissue (unstained slides or paraffin block) to the study central laboratory prior to randomization. The tumor tissue can be obtained from any organ except brain or bone and must have been biopsied no more than 2 years prior to the date of informed

consent. Alternatively, a fresh tumor sample must be obtained and shipped to the study central laboratory prior to randomization if archival tumor tissue is unavailable or inadequate.

5. Recovery to baseline or ≤ Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. Examples of exceptions are subjects with Grade 2 neuropathy or alopecia who are allowed for trial participation.
6. Age eighteen years or meeting country definition of adult, whichever is older, on the day of consent.
7. Karnofsky Performance Status (KPS) ≥ 70%.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization:
    a. Absolute neutrophil count (ANC) ≥ 1500/μL (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. Criterion intentionally left blank.
    c. Platelets ≥ 100,000/μL (≥ 100 GI/L) without transfusion within 2 weeks before screening laboratory sample collection.
    d. Hemoglobin ≥ 8 g/dL (≥ 80 g/L) without transfusion within 1 week before screening laboratory sample collection and no clinical evidence of bleeding.
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.
    f. Total bilirubin ≤ 1.5 × ULN (with the exception that total bilirubin for subjects with Gilbert's disease ≤ 3 × ULN).
    g. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 5-3 for Cockcroft-Gault formula).
    h. Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h urine protein ≤ 1 g.
9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessments except those procedures performed as standard of care within the screening window.
10. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception (defined in Appendix D) during the course of the study and for 5 months for women, and 7 months for men, after the last dose of study treatment. A barrier contraceptive method (eg, condom) is also required.
11. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman > 45 years-of-age in the absence of other biological or physiological causes. In addition, females < 55 years-of-age must have a serum follicle stimulating hormone (FSH)

level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

Exclusion Criteria

1. Prior systemic anticancer therapy for unresectable locally advanced or metastatic RCC including investigational agents.
   Note: One prior systemic adjuvant therapy is allowed for completely resected RCC and if recurrence occurred at least 6 months after the last dose of adjuvant therapy.
   Note: Adjuvant therapy with a PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor is not permitted.
2. Radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
3. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or radiosurgery and stable for at least 4 weeks prior to randomization after radiotherapy, or at least 4 weeks prior to randomization after major surgery (eg, removal or biopsy of brain metastasis). Subjects who are neurologically symptomatic as a result of their CNS disease, or are receiving systemic corticosteroid treatment (prednisone equivalent > 10 mg/day) at the planned time of randomization are not eligible.
4. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).
   a. Allowed anticoagulants are:
      i. Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
      ii. Therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor

   Note: Subjects who switch from an oral anticoagulant to LMWH are allowed if the oral anticoagulant was stopped ≥ 5 half-lives of the oral anticoagulant prior to planned randomization date.
5. Administration of a live, attenuated vaccine within 30 days prior to randomization. The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.

6. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders:

        i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, Torsades de pointes).

        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.

        iii. Stroke, transient ischemic attack (TIA), myocardial infarction, or other symptomatic ischemic event or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism [DVT/PE]) within 6 months before randomization.

            Note: Subjects with a diagnosis of DVT within 6 months are allowed if asymptomatic and stable at screening and treated with LMWH for at least 1 week before randomization.

            Note: Non-symptomatic white matter disease in the brain is acceptable.

    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra-abdominal abscess must be confirmed prior to randomization.

    c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.

    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

    e. Lesions invading major pulmonary blood vessels.

    f. Other clinically significant disorders such as:

        i. Autoimmune disease that has been symptomatic or required treatment within the past two years from the date of randomization.

            Note: Patients with a history of Crohn's disease or ulcerative colitis are always excluded.
            Note: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Note: Inhaled, intranasal, intra-articular, or topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.

iii. Active infection requiring systemic treatment. Acute or chronic hepatitis B or C infection, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or known positive test for tuberculosis infection where there is clinical or radiographic evidence of active mycobacterial infection.

iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

v. Serious non-healing wound/ulcer/bone fracture.

vi. Malabsorption syndrome.

vii. Uncompensated/symptomatic hypothyroidism.

viii. Moderate to severe hepatic impairment (Child-Pugh B or C) (Appendix J).

ix. Requirement for hemodialysis or peritoneal dialysis.

x. History of solid organ or allogeneic stem cell transplant.

xi. Known history of COVID-19 unless the subject has clinically recovered from the disease at least 30 days prior to randomization.

7. Major surgery (eg, nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks prior to randomization. Minor surgeries within 10 days prior to randomization. Subjects must have complete wound healing from major or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

8. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before randomization. Furthermore, subjects with a history of additional risk factors for torsades de pointes (eg, long QT syndrome) are also excluded.

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.

9. History of neuropsychiatric disorder likely to interfere with ability to comply with protocol requirements or give informed consent.

10. Pregnant or breastfeeding females.

11. Inability to swallow tablets or unwillingness or inability to receive IV administration.
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe infusion-related reactions to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.
13. Any other active malignancy at time of randomization or diagnosis of another malignancy within 3 years prior to randomization that requires active treatment, 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.

ESTIMATED LENGTH OF SUBJECT PARTICIPATION

It is estimated that subjects will participate for an average of approximately 12-18 months on study treatment. Subjects will be followed until death, withdrawal of consent, or Sponsor decision to no longer collect survival data.

ESTIMATED STUDY DATES

It is estimated that 21 months will be required to randomize 840 subjects. The number of events required for the primary analyses of PFS (249 events among the first 440 randomized subjects) is expected to be observed approximately 23 months after the first subject is randomized. The number of events required for the final analysis for the secondary endpoint of OS (433 events among 840 subjects) is expected to be observed approximately 69 months after the first subject is randomized. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active. The estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation.

INVESTIGATIONAL REGIMEN DOSE / ROUTE / DURATION

The first four doses of nivolumab will be administered once every 3 weeks (q3w) at 3 mg/kg over a period of 30 minutes, followed by ipilimumab at 1 mg/kg over a period of 30 minutes. After the first four doses are completed, no further ipilimumab will be given and nivolumab will be administered at a flat dose of 480 mg as an IV infusion over 30 min every 4 weeks (q4w). In this study, treatment with nivolumab will be given for a maximum of 2 years from the start of study treatment.

Subjects will also take blinded oral study medication (2 tablets containing 20 mg each of cabozantinib or placebo equivalent) once daily (qd). The subject will be fasted (with the exception of water) for at least 2 hours before receiving cabozantinib/placebo. Upon completion of the 2-hour fast, the subject will receive the oral dose of cabozantinib/placebo with a minimum of 8 oz (240 mL) of water and then the subject will continue to fast for 1 hour.

Two dose reduction levels of the oral study medication (cabozantinib or placebo equivalent) will be allowed (20 mg qd and 20 mg every other day [qod]). Dose reductions for nivolumab and ipilimumab will not be allowed and AEs will be managed by dose delays.

Subjects will continue study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for alternative systemic anticancer treatment, or other reasons for treatment discontinuation.

Nivolumab, ipilimumab, and cabozantinib/matched placebo will be supplied by the Sponsor.

EFFICACY ASSESSMENTS

Subjects will be monitored for radiographic response and progression per RECIST 1.1. For determining radiographic endpoints, radiographic assessments will be assessed by the BIRC. Radiographic assessments per RECIST 1.1 by the Investigator will be used for treatment decisions. Overall survival will be assessed at scheduled visits and every 12 weeks (± 14 days) after the FU-2 visit. Subjects will be followed until death, withdrawal of consent for non-interventional study assessments, or Sponsor decision to no longer collect these data.

TUMOR ASSESSMENTS

Chest / Abdomen / Pelvis (CAP): Computed tomography (CT) of CAP or CT chest and magnetic resonance imaging (MRI) abdomen/pelvis will be performed in all subjects at screening (prior to randomization). The first tumor assessment after randomization should be performed at W10D1 (± 7 days). Subsequent tumor assessments should be performed every 8 weeks (± 7 days) through Week 50. Upon completion of 50 weeks of radiographic assessment, these assessments will be performed every 12 weeks (± 7 days). Additional imaging of potential disease sites should be performed whenever radiographic disease progression (PD) is suspected.

Brain: MRI (or CT) of the brain will be performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis (or if clinically indicated) following the same post-baseline frequency as the imaging for CAP. MRI is the preferred method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless MRI is contraindicated. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization after radiotherapy or major surgery [eg, removal or biopsy of brain metastasis].)

Bone scans: Technetium bone scans (TBS) should be performed at screening for all subjects. After randomization, bone scans will be performed in subjects with known bone metastases and otherwise as clinically indicated per standard of care. Any soft tissue lesions associated with identified bone lesions must be imaged by CT/MRI and assessed in alignment with the CAP assessments. Bone scan findings alone cannot be used for the determination of progression or response and need to be corroborated by CT or MRI, which will be used as the basis for RECIST evaluations.

Tumor assessments should continue on the protocol-defined schedule, relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued. The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization.

Radiographic response and PD will be determined using RECIST 1.1. Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next

scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the Investigator does not necessarily warrant discontinuation of tumor assessments or study treatment.

Radiographic tumor assessments are to continue until the following criteria are met:

- For subjects who discontinue study treatment upon determination of Investigator-assessed radiographic PD per RECIST 1.1, tumor assessments may cease.
- For subjects who discontinue study treatment before Investigator-assessed radiographic PD, tumor assessments are to continue per the protocol-defined schedule until Investigator-assessed radiographic PD per RECIST 1.1.
- For subjects who continue to receive study treatment after Investigator-assessed radiographic PD because of Investigator-assessed clinical benefit which outweighs the potential risks, tumor assessments are to continue per the protocol-defined schedule until study treatment is permanently discontinued.

For the purpose of determining radiographic study endpoints, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments will be promptly sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions.

OVERALL SURVIVAL FOLLOW-UP ASSESSMENTS

Overall survival (OS) will be assessed every 12 weeks (± 14 days) after the FU-2 visit, which occurs 100 (±14) days after the date of the decision to discontinue study treatment. Subjects will be followed until death or Sponsor decision to no longer collect these data. Receipt of systemic NPACT will also be collected during follow-up contacts. If a subject withdraws consent for non-interventional study assessments, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations.

SAFETY ASSESSMENTS

Routine laboratory safety evaluations will be performed on the date of the first dose (W1D1) and every 3 weeks on nivolumab/ipilimumab dosing days (W4D1, W7D1, W10D1), and then every 4 weeks thereafter (W14D1, W18D1, W22D1 etc). Additional laboratory assessments (serum chemistry, hematology and urinalysis only) will be performed at W3D1, W6D1, W9D1, and W12D1. Routine safety follow-up visits will be performed 30 (+14) days (FU-1 visit) after the date of the decision to permanently discontinue study treatment.

Monitoring will continue for unrelated SAEs (Table 8-1) through the 100 (± 14) day (FU-2) visit after the date of decision to permanently discontinue study treatment. Related AEs leading to study treatment discontinuation, AESIs, and related SAEs will continue to be followed until resolution (event is fully resolved, ≤ Grade 2 severity, or is deemed stable/irreversible by the Investigator). Further details on AE follow up and data collection requirements are available in Appendix H.

Safety assessments will include physical examination, vital signs, performance status, 12-lead ECG, hematology, serum chemistry, coagulation tests, urine tests (including UPCR), pregnancy tests (in females of childbearing potential), and thyroid function tests. Adverse event seriousness, severity grade, relationship to study treatment, and relationship to immune effects (ie, immune-related AEs [irAEs]) will be assessed by the Investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5 (CTCAE v5).

An Independent Data Monitoring Committee (IDMC) will be established to monitor safety of the study on a regular basis. The IDMC will operate independently from the Sponsor and the clinical investigators.

Special accommodations during the global COVID-19 pandemic are described in Appendix K.

PHARMACOKINETIC ASSESSMENTS

Blood samples will be obtained from all subjects in both study arms. Samples will be collected for plasma cabozantinib concentration measurement predose on Week 1, Day 1 (W1D1), W4D1, W7D1, W10D1, and W14D1. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib in this population.

Serum concentrations of nivolumab and ipilimumab will be measured. Samples will be collected for serum nivolumab and ipilimumab concentration measurement predose on W1D1, W4D1, W7D1, W10D1, W14D1, W26D1, and FU-1 and FU-2 visits. The results will be used to confirm exposure to nivolumab and ipilimumab.

Collection of PK samples may be halted early, or sampling frequency may be reduced at the discretion of the Sponsor.

IMMUNOGENICITY ASSESSMENTS

Blood samples will be obtained from all subjects in both study arms for immunogenicity assessment (anti-drug antibodies [ADA] for nivolumab and ipilimumab) predose on W1D1, W14D1, W26D1, and FU-1 and FU-2 visits. Samples will be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab if ADA testing is positive.

BIOMARKER ASSESSMENTS

Peripheral blood and tumor tissue will be collected and may be assessed for exploratory biomarker analyses. Tumor tissue (fresh, or archival [ie, within 2 years prior to the date of informed consent]) will be obtained once consent is provided and shipped to central laboratory for analysis. PD-L1 expression by IHC of tumor will be determined.

For assessment of PD-L1 expression, evaluation of at least 100 viable tumor cells is required. Positive staining is defined as ≥ 1% and negative staining is defined as < 1% of cells that exhibit circumferential and/or partial linear plasma membrane staining at any intensity. High cytoplasmic staining can interfere with membrane scoring and will define as “indeterminate”. Additionally, failure of PD-L1 staining due to suboptimal tissue sample integrity or assay failure will also be defined as “indeterminate”.

Peripheral blood samples will be obtained pre-dose and on days as specified in the Schedule of Assessments. Optional tumor biopsies may be collected approximately 6 weeks after the first dose of study treatment.

Exploratory analyses may include, but may not be limited to, the following:

- PD-L1 and MET and other relevant biomarkers in tumor specimens for association with clinical outcomes
- T-cell infiltration and tumor gene expression (ie, mutational load assessment) in tumor specimens for association with clinical outcome
- Circulating immune cells in peripheral blood (ie, lymphocyte subset analyses by flow cytometry)
- Plasma biomarkers (ie, cytokines/chemokines, VEGF, metabolome)
- Tumor whole-genome sequencing and gene expression analysis
- Cell and/or pharmacogenomic analyses (ie circulating tumor DNA [ctDNA])

Collection of biomarker samples (with the exception of PD-L1 assessments) may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Subjects will be requested to complete the EuroQol Health questionnaire instruments EQ-5D-5L during screening and every 3 weeks after randomization until W10D1 and every 4 weeks thereafter. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or the study meets its primary endpoint. Subjects are to complete the questionnaires prior to each clinic visit. HRQOL assessments will no longer be collected for subjects if the study transitions to the Maintenance Phase.

HEALTH CARE RESOURCE UTILIZATION

Health care resource utilization parameters will be collected from randomization through the FU-2 visit. These include hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions. These data will not be collected in the Maintenance Phase.

STATISTICAL METHODS

The primary efficacy endpoint in this study is BIRC-determined PFS. Treatment with cabozantinib in combination with nivolumab and ipilimumab will be inferred to be superior to treatment with nivolumab and ipilimumab if the null hypothesis of no difference between arms in duration of PFS is rejected.

In the primary analysis, PFS is defined as the time from randomization to the earlier of either radiographic PD per RECIST 1.1 as determined by the BIRC or death from any cause.

The study is designed to provide adequate power for both PFS (primary endpoint) and OS (secondary endpoint). A larger sample size is needed to provide reasonable power to evaluate OS

than for PFS. Thus, to allow longer, more robust PFS follow up among a fewer number of subjects and to avoid biasing the events included in the PFS analysis towards shorter event times, the study will employ a "trial within a trial" design (Hessel et al 2016); the event-driven primary analysis of PFS will be conducted after at least 249 PFS events have been observed among the first 440 randomized patients, defined as the PFS Intent-to-Treat (PITT) population. This will provide the study with 90% power to reject the null hypothesis of no difference in PFS using a 2-sided log-rank test with a 5% level of significance assuming a true HR of 0.66. Assuming an exponential distribution of PFS, this corresponds with a 52% increase in median PFS from 11.6 months to 17.6 months. In the current design, the minimum observed effect that would result in statistical significance for PFS is an HR of 0.78, a 28% improvement in median PFS from 11.6 to 14.9 months.

For the secondary endpoint of improving duration of OS, the trial was originally designed as follows: a total of 342 events among 676 randomized subjects (the ITT population) are required to provide 90% power to reject the null hypothesis of no difference in OS using the log-rank test at the 2-sided significance level of 5%, 3 planned interim analyses (see Section 9.6), and assuming a true HR of 0.70 . Assuming an exponential distribution for OS, this corresponds to a 43% increase in median survival from 41 months to 58.6 months. Under this design the minimum observed effect that would result in statistical significance for OS is an HR of 0.80, a 25% improvement in median from 41 to 51.1 months; a minimum observed difference in medians of approximately 10 months.

In response to new data supporting a median OS in the control arm of 48 months instead of the previously assumed 41 months (Albiges et al 2020), the study has been modified as follows: a total of 433 events among 840 randomized subjects (the ITT population) are required to provide 90% power to reject the null hypothesis of no difference in OS using the log-rank test at a 2-sided significance level of 5%, 3 planned interim analyses (see Section 9.6), and assuming a true HR of 0.73. Assuming an exponential distribution for OS, this corresponds to a 37% increase in median survival from 48 months to 65.8 months. Under this design the minimum observed effect that would result in statistical significance for OS is an HR of 0.824, a 21% improvement in median from 48 to 58.25 months; a minimum observed difference in medians of approximately 10 months.

This increase in sample size does not inflate Type 1 error because (a) it was done solely in response to new external data about the expected median OS of the control arm, and (b) the control arm median is a nuisance parameter with respect to the minimum observed difference in medians that results in rejection of the null hypothesis. This change ensures the trial retains the ability to reject the null hypothesis for OS if the observed difference in medians is approximately 10 months.

Inflation of Type 1 error associated with testing multiple endpoints (primary and secondary) will be controlled by applying a hierarchical testing procedure: OS will be tested only if the null hypothesis of no difference between arms in PFS is rejected. Three interim analyses of OS are planned and will include the entire ITT population available at the time of each analysis. The first, conducted at the time of the primary PFS analysis (if the null hypothesis for PFS is rejected), is anticipated to include 27% of the total deaths necessary for the primary analysis of OS (ie, 27% information fraction). This is intended primarily as an administrative analysis to provide a qualitative evaluation of OS at the time of the primary PFS analysis. Subsequent

interim analyses of OS are planned at the 50% and 75% information fractions. Inflation of Type 1 error associated with these interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

To help limit exposure to the experimental regimen should interim data suggest it is unlikely to demonstrate superior efficacy, a non-binding futility analyses of PFS per BIRC is planned to be performed at the 40% information fraction for PFS. Further details are provided in Section 9.6.

PFS and OS will be summarized descriptively using the Kaplan-Meier method. Inferential comparisons between treatment arms will use the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. Primary stratification analyses will be based on the stratification factors used for the randomization as recorded in the interactive response technologies (IRT) system.

With an assumed constant accrual rate of 40 subjects per month, a 1:1 treatment allocation ratio, and 3 interim analyses of OS, a total of 840 subjects (420 per treatment arm) are required to observe the required number of events within the planned study duration: approximately 21 months accrual; approximately 23 months after first subject randomized to observe the required PFS events among the first 440 subjects and approximately 69 months after first subject randomized to observe the required deaths for OS among 840 subjects. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active.

The PITT population may be expanded by 25% from the first 440 to the first 550 randomized if a review of accumulating PFS events suggests that the 249 events required for the analysis will not be reached due to censoring caused by a higher than expected study drop-out or non-compliance stemming from the COVID-19 pandemic.

Study Completion:

The study will be considered complete if any of the following criteria apply:

- futility analysis of PFS: the trial has been declared futile by the Sponsor, or
- primary analysis of PFS: null hypothesis is not rejected, or
- primary analysis of PFS: null hypothesis is rejected for PFS and the null hypothesis is rejected for OS (or the final planned analysis for OS has been conducted).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-vs-time curve
BIRC	blinded independent radiology committee
BP	blood pressure
BUN	blood urea nitrogen
CAP	chest/abdomen/pelvis
CAP	chest/abdomen/pelvis
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CYP	cytochrome P450
DICOM	Digital Imaging and Communications in Medicine
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DVT	deep vein thrombosis
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ESC	Executive Safety Committee
FACS	fluorescence-activated cell sorting

Abbreviation or Term	Definition
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU-1	Post-Treatment Follow-up Visit #1
FU-2	Post-Treatment Follow-up Visit #2
GCP	Good Clinical Practice
GGT	γ-glutamyltranspeptidase
GI	gastrointestinal
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
ICI	immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IMDC	International mRCC Database Consortium
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	interactive response technologies
ITT	intent-to-treat
IV	intravenous
KPS	Karnofsky performance status
LDH	lactate dehydrogenase
LLN	lower limit of normal
LMWH	low molecular weight heparins
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MI	myocardial infarction
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging

Abbreviation or Term	Definition
MRP2	multidrug resistance-associated protein 2
MSKCC	Memorial Sloan-Kettering Cancer Center
MTC	medullary thyroid cancer
NCI	National Cancer Institute
NE	not evaluable
NPACT	nonprotocol anticancer therapy
NSCLC	non–small-cell lung cancer
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death receptor-1 ligand
PE	pulmonary embolism
PFS	progression-free survival
PITT	PFS Intent-to-Treat
PK	pharmacokinetic or pharmacokinetics
PPE	palmar-plantar erythrodysesthesia
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
qnw	once every n weeks
qod	every other day
QTcF	Corrected QT interval calculated by the Fridericia formula
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome (preferred term: posterior reversible encephalopathy syndrome [PRES])
RSI	reference safety information
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJS	Suspected Stevens-Johnson syndrome

Abbreviation or Term	Definition
SNP	single nucleotide polymorphism
SoD	sum of the diameters
T4	thyroxine
TAM	tumor-assisted macrophage
TBS	technetium bone scan
TEN	Toxic Epidermal Necrolysis
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
Treg	regulatory T-cell
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)
VHL	von Hippel-Lindau
W1D1	Week 1 Day 1
WBC	white blood cell

1 BACKGROUND

1.1 Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the eighth most common cancer in the world. RCC accounts for 90% to 95% of malignant neoplasms arising from the kidney. Globally, over 330,000 cases of RCC are reported each year with over 100,000 deaths occurring as a result of progression of metastatic disease (Znaor et al 2015). In the United States, there are approximately 65,000 new cases each year and about 15,000 deaths from RCC annually (Siegel et al 2018). Recent advances in surgical and systemic therapies have significantly changed the management of RCC. However, the rate of RCC-related mortality has increased despite earlier detection of smaller kidney tumors (Sun et al 2011; Hollingsworth et al 2006). 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) and mammalian target of rapamycin (mTOR) pathways have been found to be important targets in RCC disease. Multiple drugs targeting these pathways have been approved, including cabozantinib which targets the VEGF pathway and other receptor tyrosine kinases (RTKs; Banumathy and Cairns 2010, Section 1.2). More recently treating cancer with immunotherapies has also expanded treatment options. Nivolumab, a programmed death receptor 1 (PD-1) antibody, is the only immune checkpoint inhibitor (ICI) indicated for the treatment of relapsed disease (Opdivo™ US PI). Recently, the results of the Checkmate-214 trial (Motzer et al 2018) led to approval in the US and other regions of nivolumab in combination with ipilimumab for patients with intermediate- or poor-risk, previously untreated advanced RCC (Section 1.5), which constitutes the control arm of this study.

Several academic groups have identified variables associated with survival and created prognostic models in metastatic RCC (mRCC). These risk models are commonly used for choosing therapies or selecting patients for treatment in clinical trials. The International mRCC 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 (Heng et al 2009). Historically, agents for previously untreated patients with mRCC have been associated with median overall survival (OS) of 43.2 months in patients with favorable risk disease (which accounts for approximately 25% of all untreated mRCC), 22.5 months in those with intermediate risk disease (which accounts for approximately 50% of all untreated mRCC) and only 7.8 months in those with poor risk disease according to IMDC criteria (Heng et al 2013).

1.2 Cabozantinib

Cabozantinib (XL184) is a potent inhibitor of multiple RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization including the VEGF receptor (VEGFR), MET, AXL, and RET. Inactivation of the von Hippel-Lindau (VHL) tumor suppressor protein in clear cell RCC results in upregulation of VEGF, MET, and AXL. Increased expression of MET and AXL has been associated with poor prognosis in RCC (Gibney et al 2013, Zhou et al 2016, Ciamporcero et al 2015). In addition, targets of cabozantinib, including TYRO3, MER, and AXL (TAM family kinases), are implicated in promoting suppression of an antitumor immune response. Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment, which might present an opportunity for synergistic effects from combination treatment with immune checkpoint inhibitors (ICIs) independent of tumor programmed death receptor-1 ligand (PD-L1) expression.

Cabozantinib (60 mg, tablets) has been compared with everolimus in patients with advanced RCC who had received prior therapy with at least one VEGFR-tyrosine kinase inhibitor (VEGFR-TKI) in multicenter, randomized, open-label, controlled Phase 3 study (METEOR; Choueiri et al 2015, Choueiri et al 2016). In this trial, 658 subjects were randomized to receive cabozantinib (n = 330) or everolimus (n = 328). After a minimum follow-up of 11 months in the first 375 randomized subjects, the primary endpoint of progression-free survival (PFS) by blinded independent radiology committee (BIRC) was 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm (hazard ratio [HR] 0.58 [95% confidence interval {CI} 0.45, 0.75]; p-value < 0.001). Objective response rate (ORR) per BIRC was 17% in the cabozantinib arm vs 3% in the everolimus arm (p-value < 0.001). An interim OS analysis at the time of this final PFS analysis demonstrated a trend toward longer OS (HR = 0.67, p-value = 0.005; p-value ≤ 0.0019 required for statistical significance). A subsequent OS analysis, performed after a median follow-up of approximately 19 months in all 658 randomized subjects, demonstrated a significant improvement in OS, with median OS of 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm (HR = 0.66 [95% CI 0.53, 0.83]; p-value = 0.00026). Subgroup analyses of PFS and OS based on a range of demographic and baseline characteristics were consistent with the results for the overall population. Grade 3-4 adverse reactions and laboratory abnormalities that occurred in ≥ 5% of cabozantinib-treated patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia (PPE), hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, hypokalemia, and γ-glutamyltranspeptidase (GGT) increased (Cabometyx™ US PI).

Cabozantinib (60 mg, tablets) has also been compared with sunitinib in previously untreated advanced RCC patients in a randomized Phase 2 study (CABOSUN; Choueiri et al [Ann Oncol] 2017, Choueiri et al [Eur J Cancer] 2018). In this trial, subjects were required to have either intermediate or poor risk disease according to IMDC criteria and were randomized in 1:1 ratio to receive either cabozantinib (n = 79) or sunitinib (n = 78). The primary endpoint in this trial was PFS. Compared with sunitinib, cabozantinib treatment significantly increased median PFS per BIRC (8.6 vs 5.3 months) and was associated with a 52% reduction in rate of progression or death (adjusted HR = 0.48; 95% CI 0.31, 0.74; two-sided p-value = 0.0008). The ORR per BIRC was 20% (95% CI 12.0, 30.8) for cabozantinib vs 9% (95% CI 3.7, 17.6) for sunitinib. For the analysis of the secondary endpoint of OS, only available data through 13 January 2017 were used. Kaplan-Meier estimates for median duration of OS were 30.3 months in the cabozantinib arm vs 21.0 months in the sunitinib arm (adjusted HR = 0.74; 95% CI 0.47, 1.14). The median time of follow up for OS was 28.9 months. A subsequent analysis of OS with data through 01 July 2017 was consistent with the prior results (adjusted HR = 0.80; 95% CI 0.53, 1.21; Choueiri et al [Eur J Cancer] 2018). The most frequent Grade 3-4 adverse reactions (≥5%) in cabozantinib-treated patients were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, alanine aminotransferase (ALT) increased, decreased appetite, stomatitis, pain, hypotension, and syncope.

Cabozantinib (60 mg, tablets) is approved in the US for the treatment of patients with advanced RCC and in the EU for the treatment of adult patients with advanced RCC after prior VEGF-targeted therapy or treatment-naïve adult patients with intermediate or poor risk RCC (Cabometyx™ US PI and EMA SmPC). Cabozantinib (60 mg, tablets) is also approved in the US and EU for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (Cabometyx US PI and EMA SmPC), based on the results of a randomized, double-blind, placebo-controlled, multicenter trial showing that treatment with cabozantinib was associated with statistically significant improvements in OS, PFS and ORR.

Cabozantinib (140 mg, capsules) is also approved in the US and in the EU, for the treatment of progressive, metastatic medullary thyroid cancer (MTC; Cometriq™ US PI and EMA SmPC). This was based on the results of a multicenter, randomized, double-blind, controlled Phase 3 study comparing cabozantinib (140 mg, capsules) with placebo in which cabozantinib demonstrated a statistically significant improvement of the primary endpoint of PFS (Elisei et al 2013). The capsule and tablet formulations are not bioequivalent or interchangeable.

1.3 Nivolumab

Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) kappa antibody that is specific for the human PD-1 cell surface membrane receptor, a negative regulatory molecule expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Through the inhibition of the interaction of PD-1 with its ligands (PD-L1 and PD L2), nivolumab has demonstrated the ability to generate increased anti-tumor immune responses and improvements in survival of cancer patients. Single-agent nivolumab has been approved in multiple cancer types including patients with advanced RCC after prior antiangiogenic therapy in the US and in patients with advanced RCC after prior therapy in Europe (Opdivo™ US PI and EMA SmPC). Approval was based on the clinical activity of nivolumab observed in a large Phase 3 trial conducted in 821 subjects with advanced RCC previously treated with 1 or 2 anti-angiogenic therapies who were randomized to receive nivolumab 3 mg/kg every 2 weeks (q2w) or everolimus 10 mg once-daily (qd) (CheckMate-025, NCT01668784; Motzer et al 2015). A planned interim analysis, after a minimum of follow-up of 14 months, demonstrated a statistically significant and clinically meaningful improvement in OS of nivolumab monotherapy vs everolimus (median OS, 25.0 months vs 19.6 months, respectively; HR = 0.73 [98.5% CI 0.57, 0.93]; p-value = 0.002). ORR was 25% for nivolumab vs 5% for everolimus. In an assessment of OS by favorable-, intermediate-, and poor-risk IMDC groups, OS benefit for nivolumab over everolimus was observed across all subgroups (Escudier et al 2017). However, greater benefit was observed in the intermediate- (HR = 0.73; 95% CI 0.56, 0.95) and poor-risk subgroup (HR = 0.60; 95% CI 0.42, 0.86) versus the favorable-risk subgroup (HR = 0.79; 95% CI 0.39, 1.58). The most common adverse reactions (reported in at least 20% of nivolumab-treated patients) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia.

1.4 Ipilimumab

Ipilimumab is a fully-human monoclonal IgG1 kappa antibody that binds to the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antigen expressed on a subset of human T cells. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA4/B7 interaction. Single-agent ipilimumab is approved in the US and Europe for the treatment of unresectable or metastatic melanoma (Yervoy™ US PI and EMA SmPC).

Ipilimumab monotherapy for the treatment of mRCC refractory to or ineligible for interleukin-2 was studied in Phase 2 clinical trial MDX010-11 (NCT00057889). Two sequential cohorts were studied, each with a loading dose of 3 mg/kg followed by 3 doses of either 1 mg/kg (group 3-1; n = 21) or 3 mg/kg (group 3-3; n = 40). Patients with stable disease (SD) or a partial response (PR) or complete response (CR) were allowed additional treatment. Many patients received more than the conventional 4 doses of ipilimumab. In Group 3-1 (n = 21), 1 patient (5%) had a PR (Yang et al 2007). In Group 3-3 (n = 40), 5 patients (12.5%) had a PR. Among 14 previously untreated patients in Group 3-3, 3 (21%) had a PR. The major toxicities were colitis (all Grade 3 and 4; 14% in Group 3-1, 33% in Group 3-3) and hypophysitis (1 Grade 3/4, 1 Grade 1/2 in Group 3-3; none in Group 3-1). Most reported adverse events (AEs) were Grade 1/2 (57% in Group 3-1, 35% in Group 3-3) or Grade 3 (38% in Group 3-1, 48 % in Group 3-3). There were 6 patients (15%) with Grade 4 AEs in Group 3-3. The most common treatment related AEs in Group 3-1 (total 81%) and Group 3-3 (total 93%) were diarrhea (38% and 40%, respectively) and fatigue (33% and 38%, respectively). Most AEs were manageable with appropriate treatment, including high dose corticosteroids and hormone replacement.

1.5 Combination Therapy of Nivolumab and Ipilimumab

Nivolumab and ipilimumab have been evaluated in combination in previously untreated locally advanced or metastatic RCC subjects. In a Phase 1 study nivolumab and ipilimumab were evaluated in combination at various doses (CheckMate-016; Hammers et al 2017). In this trial approximately half of the enrolled subjects were previously untreated and most were favorable risk (~45%) or intermediate risk (~48%) per Memorial Sloan Kettering Cancer Center (MSKCC) criteria. The same ORR of 40.4% was reported for the combination of nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3I1) as well as for nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1I3). Median OS was not reached (95% CI 26.7 months, not evaluable [NE]) in the N3I1 arm and 32.6 months (95% CI: 26.0 months, NE) in patients in the N1I3 arm. At 12 and 24 months, OS was 81% and 67% in the N3I1 arm and 85% and 70% in the N1I3 arm, respectively (Hammers et al 2017).

In a randomized Phase 3 trial (CheckMate 214, Motzer et al 2018), 1096 subjects with previously untreated advanced RCC were randomized to receive nivolumab+ipilimumab (nivo+ipi; n=550) or sunitinib (n=546). The primary endpoints were OS, PFS per BIRC, and ORR per BIRC in the IMDC intermediate- and poor-risk subjects. At a median follow-up of 25.2 months, the 18-month OS rate was 75% (95% CI 70, 78) with nivo+ipi vs 60% (95% CI 55, 65) with sunitinib; the median OS was not reached with nivo+ipi vs 26.0 months with sunitinib (HR = 0.63 [95% CI 0.44, 0.89]; p-value < 0.001; by interpolation median OS for the nivo+ipi

arm is estimated to be approximately 41 months). The median PFS by BIRC in the intermediate- and poor-risk population was 11.6 months vs 8.4 months (HR 0.82 [95% CI 0.64, 1.05]; p-value = 0.03). With extended follow-up in intermediate-risk or poor-risk patients, results for all three primary efficacy endpoints now show that nivolumab plus ipilimumab continue to be superior to sunitinib (Motzer et al 2019). The ORR in this population was 42% (9% CR) for the nivo+ipi arm vs 27% (1% CR) for the sunitinib arm. Higher expression of PD-L1 (≥1%) was associated with greater magnitude of benefit in survival in the intermediate- and poor-risk population with an HR for OS of 0.45 (95% CI 0.29, 0.71; p-value < 0.001) for the PD-L1 subgroup ≥ 1% vs 0.73 (95% CI 0.56, 0.96; p-value = 0.0249) for the PD-L1 < 1% subgroup. A similar trend was observed in terms of response rate with an ORR of 58% for nivo+ipi vs 22% for sunitinib in PD-L1 ≥ 1% and an ORR of 37% for nivo+ipi vs 26% for sunitinib in PD-L1 <1%. There was no PFS benefit observed in the PD-L1 < 1% sub-group in the intermediate- and poor-risk patients. A statistically significant difference was observed for survival in the Intent-to-Treat (ITT) population (secondary endpoint) with median OS not reached in the nivo+ipi arm vs 32.9 months for the sunitinib arm (HR 0.68 [95% CI 0.49, 0.95]; p-value = 0.0003). Of note, there was no benefit in terms of response rate or PFS in the IMDC favorable risk population: sunitinib was superior to the combination of nivolumab and ipilimumab (ORR of 29% for nivo + ipi versus 52% for sunitinib; PFS of 15.3 months for nivo+ipi vs 23.1 months for sunitinib). The most common adverse reactions (reported in at least 20% of all nivo+ipi-treated patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite (Opdivo US PI). The results from this study led to approval in the US and other regions of nivolumab in combination with ipilimumab for patients with intermediate or poor risk, previously untreated advanced RCC (Opdivo US PI /SmPC and Yervoy US PI/SmPC). Based on 4 years of follow-up, the median OS for the active arm (nivolumab plus ipilimumab) in intermediate or poor risk subjects was reported to be 48.1 months (Albiges et al 2020), approximately 7 months longer than originally projected for the control arm in the COSMIC-313 study.

1.6 Combination Therapy of Cabozantinib with Nivolumab or Cabozantinib with Nivolumab and Ipilimumab

Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in patients with urothelial cancer (UC; Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment, which might present an opportunity for synergistic effects from combination treatment with ICIs. *In vitro* and *in vivo* experiments employing a murine colon carcinoma cell line (MC38-CEA) demonstrated that cabozantinib treatment altered immune modulation and

immune subset conditioning (Kwilas et al 2014). Specifically, treatment of tumor cells with cabozantinib in vitro led to increased tumor-cell expression of major histocompatibility complex (MHC) class 1 antigen and greater sensitivity of tumor cells to T-cell-mediated killing. In a mouse MC38-CEA tumor model, cabozantinib treatment led to increased peripheral CD8+ T-cell counts, decreased regulatory T-cells (T_{reg}) and myeloid-derived suppressor cells (MDSCs), and decreased T_{reg} suppressor activity. Furthermore, synergistic effects including increased CD8+ T cell infiltration and decreased infiltration by MDSCs and tumor-assisted macrophages (TAMs) were observed when a poxviral-based cancer vaccine was administered in addition to cabozantinib in the mouse tumor model. Further, robust synergistic effects of the combination of cabozantinib with antibodies against PD-1/PD-L1 and CTLA4 were demonstrated in a castration-resistant prostate cancer mouse model by suppression of MDSC-promoting cytokines (Lu et al 2017).

The reductions in T_{reg} cells following treatment with cabozantinib was also observed in subjects with advanced refractory urothelial cancer (UC; discussed below; Apolo et al 2014). In addition, in subjects with metastatic triple-negative breast cancer who received salvage therapy with cabozantinib, a persistent increase of circulating CD3+ cells and a persistent decrease of CD14+ monocytes were observed possibly reflecting activation of systemic antitumor immunity (Tolaney et al 2017). Together, the preclinical and clinical observations suggest that cabozantinib promotes an immunopermissive environment, which might present an opportunity for synergistic effects from combination treatment with PD-1 targeting ICIs independent of tumor PD-L1 expression.

In an ongoing Phase 1 study, the combination of cabozantinib with nivolumab and ipilimumab is being evaluated in subjects with previously treated advanced genitourinary cancers, including UC and RCC (Apolo et al [Ann Oncol] 2016, Nadal et al 2017, Nadal et al 2018). The combination of cabozantinib with nivolumab is referred to as doublet and the combination of cabozantinib with nivolumab and ipilimumab is referred to as triplet. In the dose escalation stage of the study, no dose limiting toxicities (DLTs) were reported for either the doublet or triplet combination. The recommended Phase 2 dose (RP2D) for the doublet was cabozantinib 40 mg administered orally with nivolumab 3 mg/kg administered intravenously (IV) and the RP2D for the triplet was cabozantinib 40 mg qd with nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV (maximum 4 doses). Data are available for a total of 78 subjects enrolled in this trial, including 14 subjects with RCC. The ORR for 13 RCC subjects evaluable for response for either the doublet or triplet combination was 54% (7 responders of 13 subjects). The remaining RCC subjects evaluable for response (6 of 13) had stable disease (SD) reported as their best response

to date. There was a pronounced effect on PFS and OS: median PFS in these RCC subjects was 18.4 months (95% CI 6.4, 18.4) and the median OS was not reached. Most frequent treatment-related Grade 3 or 4 AEs across all genitourinary cancer indications and dose levels for the triplet therapy (n=29) included hypertension (10%), diarrhea (10%), fatigue (7%), anorexia (3%), mucositis (3%), proctitis (3%) and thromboembolic events (3%). Two cases of hepatitis (Grade 3 or 4) and one case of immune-related colitis (Grade 3 or 4) were reported for the triplet therapy. Grade 3 or 4 laboratory abnormalities reported in subjects treated with the triplet therapy across all explored dose levels included hypophosphatemia (n=6), increased lipase (n=4), decreased lymphocyte count (n=4), hypokalemia (n=3), ALT increased (n=3), aspartate aminotransferase (AST) increased (n=3), hyponatremia (n=2), amylase increased (n=2), hypocalcemia (n=1), and decreased platelet counts (n=1). There were no Grade 5 AEs.

The ongoing randomized, open-label, Phase 3 CheckMate 9ER study (CA2099ER; NCT03141177) evaluated cabozantinib in combination with nivolumab versus sunitinib in subjects with previously untreated advanced or metastatic RCC of all IMDC risk categories. This study recently reported that cabozantinib in combination with nivolumab improved PFS (HR 0.51 [95% CI 0.41, 0.64], $P < 0.0001$; median, 16.6 vs 8.3 mo) and OS (HR 0.60 [98.89% CI 0.40, 0.89]; $P = 0.0010$; medians not reached) versus sunitinib in previously untreated advanced renal cell carcinoma (Choueiri et al 2020). These results were consistent across all prespecified IMDC risk and PD-L1 subgroups. Furthermore, the ORR (95% CI) was significantly higher with cabozantinib in combination with nivolumab compared to sunitinib (55.7% [50.1-61.2] vs 27.1% [22.4-32.3]; $P < 0.0001$), and 8.0% versus 4.6% of patients achieved complete response. Median duration of response was 20.2 months for patients treated with cabozantinib in combination with nivolumab compared to 11.5 months for patients treated with sunitinib.

CheckMate 9ER initially included a cabozantinib/nivolumab/ipilimumab (‘triplet’) arm which stopped enrollment after nivolumab /ipilimumab demonstrated improved OS versus sunitinib in the Phase 3 CheckMate 214 study (NCT02231749; Motzer et al 2018). According to a preliminary report, 46 subjects were randomized to the triplet combination in the CheckMate 9ER study. Of these 46 subjects, 36 (78%) had a Karnofsky performance status (KPS) score of 90 to 100, and the IMDC prognostic score was favorable for 11 (24%), intermediate in 27 (59%), or poor in 8 (17%). Forty-four (96%) of these subjects actually received triplet treatment, and 36 (82%) of those 44 were continuing to receive study treatment per data received on 10 July 2018. Two (4.5%) of the 44 subjects had died [PD (1), other reason (1)]. Serious adverse events were reported in 10 (23%) of the 44 subjects, including the following system organ classes:

hepatobiliary (hepatitis [2], cholangitis [1], drug-induced liver injury [1], hepatotoxicity [1], immune-mediated hepatitis [1]), investigations (ALT increased [1], AST increased [1]), pneumocystis jirovecii infection (1), pneumonia (1), rash (1), thrombocytopenia (1), myocardial infarction (1), and ischemic stroke (1). The most common AEs overall among these 44 subjects were fatigue (9) or asthenia (7), ALT increased (10), rash (10), nausea (8), decreased appetite (8), diarrhea (8), mucosal inflammation (8), hepatotoxicity (7), AST increased (7), palmar-plantar erythrodysaesthesia (7), cough (6), dysgeusia (6), and myalgia (6). AEs leading to treatment discontinuation were reported in 9 (20.5%) of the 44 subjects, including ALT increased (4), AST increased (3), amylase increased (1), blood alkaline phosphatase (ALP) increased (1), γ-glutamyltranspeptidase (GGT) increased (1), lipase increased (1), drug-induced liver injury (1), hepatitis (1), hepatotoxicity (1), diarrhoea (1), asthenia (1) and ischemic stroke (1).

1.7 Rationale

1.7.1 Rationale for Evaluating Cabozantinib in Combination with Nivolumab and Ipilimumab in IMDC Intermediate- and Poor-Risk RCC

Cabozantinib approval in the US and in the EU includes the population of treatment-naïve advanced RCC patients of IMDC intermediate- or poor-risk. More recently, the nivolumab with ipilimumab combination also received approval in the US and in the EU for previously untreated advanced RCC patients of IMDC intermediate- or poor-risk. The combination of cabozantinib with nivolumab and ipilimumab ("triplet") was initially evaluated against sunitinib in the CheckMate 9ER RCC study, but enrollment in this triplet combination was closed after the combination of nivolumab with ipilimumab was shown to be superior to sunitinib in the CheckMate 214 RCC study.

In the Phase 3 CheckMate 214 study, the combination of nivolumab with ipilimumab showed efficacy in previously untreated intermediate- and poor-risk RCC subjects (NCT02231749; Motzer et al 2018). However, there was only modest clinical benefit for this therapy in the subgroup of subjects with low PD-L1 (PD-L1 < 1%), which accounts for approximately two thirds of the patient population. Patients with low PD-L1 may respond well to VEGF-targeted agents. Therefore, combination of nivolumab and ipilimumab with cabozantinib is attractive because of the potential for improved clinical outcomes for all subjects irrespective of PD-L1 expression (Apolo et al 2014). Further evaluation of cabozantinib in combination with nivolumab and ipilimumab in previously untreated RCC patients of intermediate- and poor-risk is warranted.

The current Phase 3 study evaluates the efficacy and safety of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in previously untreated subjects with locally advanced or metastatic RCC of intermediate- or poor-risk (as defined by IMDC criteria).

1.7.2 Rationale for Study Design

This is a randomized, double-blind, controlled Phase 3 study of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in previously untreated subjects with advanced or metastatic RCC of intermediate- or poor-risk (as defined by IMDC criteria). The primary endpoint is PFS evaluated by a blinded independent radiology committee (BIRC). PFS is an accepted regulatory and clinical endpoint for studies with cancer patients including advanced RCC: several agents including sunitinib, pazopanib, and cabozantinib were approved by regulatory agencies for previously untreated patients with advanced RCC based on an increase in PFS. While OS remains a "gold standard" for oncology trials, there are now multiple active therapies approved for previously treated patients. Subsequent treatment with these agents (which could include single-agent cabozantinib) could confound the effect on OS in previously untreated patients. Therefore, PFS remains an important indicator of clinical benefit in first-line mRCC and has been chosen as the primary endpoint for this trial with OS as the secondary endpoint. Masking (blinding) oral study medication in the experimental and control arms and use of a BIRC for assessment of radiographic endpoints will minimize the potential for bias and help ensure that both study arms are treated and assessed similarly throughout the trial. Crossover between treatment arms will not be allowed.

In this study, subjects with favorable-risk disease are not being enrolled. Based on recent data for the combination of nivolumab and ipilimumab as described above in Section 1.5, clinical benefit was not demonstrated for the combination of nivolumab and ipilimumab relative to sunitinib in the IMDC favorable risk population (CheckMate-214, Motzer et al 2018).

Region is included as a stratification factor to account for differences in standard-of-care therapies for advanced RCC. Ensuring balance by region should ensure reasonable similarity in new treatments upon progression, thereby strengthening the likelihood of an unbiased assessment of OS.

PD-L1 is considered an immune-related biomarker that can be expressed on tumor cells and immune cells. Previous clinical studies have suggested that PD-L1 expression levels may have an impact on clinical outcomes of ICI therapy. In the Phase 3 study of nivolumab in combination with ipilimumab described above in Section 1.5 (CheckMate-214; Motzer et al 2018), higher

expression of PD-L1 (≥1%) was associated with greater magnitude of clinical benefit in the intermediate- and poor-risk population. Addition of cabozantinib may improve the outcome for patients with low PD-L1 expression (Apolo et al [Ann Oncol] 2016). Tumor PD-L1 status is not included as a stratification factor at randomization as it was deemed impractical to delay treatment for subjects with previously untreated advanced or metastatic RCC until the results of PD-L1 testing from the central laboratory were available before being able to enroll in the study if eligible.

In order to comprehensively evaluate the clinical effect of the combination therapy of cabozantinib with nivolumab and ipilimumab, the current Phase 3 study includes analyses of health-related quality of life (HRQOL), health care resource utilization, pharmacokinetics, and biomarkers.

1.7.3 Rationale for Study Treatment Dose Selection and Treatment Schedule

In this Phase 3 study, the cabozantinib dose will be 40 mg qd based on results from the ongoing Phase 1 study evaluating cabozantinib in combination with nivolumab as described in Section 1.6 (Apolo et al [Ann Oncol] 2016, Nadal et al 2017, Nadal et al 2018). The RP2D of nivolumab and ipilimumab (for triplet therapy) in this Phase 1 study was 3 mg/kg and 1 mg/kg, respectively (maximum of 4 doses of ipilimumab), followed by nivolumab 3 mg/kg monotherapy. Nivolumab 3 mg/kg administered q2w has been shown to be similar to a 240 mg flat dose q2w which has been approved based on clinical data and modeling and simulation approaches using population PK and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], RCC, and UC where body weight normalized dosing (mg/kg) has been used. Recently, a flat dose of nivolumab at 480 mg given q4w was determined to be equivalent to the 240 mg dose q2w and was approved by the US FDA for most nivolumab indications including RCC (Opdivo™ US PI). Therefore, in accordance with the current US PI, nivolumab will be administered at a dosing regimen of 480 mg q4w after the first four doses of nivolumab and ipilimumab administered q3w.

Previous clinical studies with ICIs suggest that there may be minimal benefit in extending treatment beyond a total of 2 years (Herbst et al 2016; Robert et al 2017; Spigel et al 2017). Therefore, in the current study, treatment with nivolumab will be given for a maximum of 2 years from the start of study treatment. Subjects will be allowed to receive treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for subsequent systemic anti-cancer

treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.6).

1.8 Overall Risk Benefit Assessment

Renal cell carcinoma (RCC) is the eighth most common cancer in the world. RCC accounts for 90% to 95% of malignant neoplasms arising from the kidney. Over 330,000 cases of RCC are reported each year worldwide with over 100,000 deaths occurring as a result of progression of metastatic disease (Znaor et al 2015). There remains a need for additional therapies and the opportunity to improve outcomes for this patient population.

Cabozantinib is a potent inhibitor of multiple RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, AXL, and RET. Cabozantinib tablets (60 mg) are approved in the US for the treatment of patients with advanced RCC and in the EU for the treatment of adult patients with advanced RCC after prior VEGF-targeted therapy or treatment-naïve adult patients with intermediate or poor risk RCC (Cabometyx™ US PI and EMA SmPC). Approval was based on improvement in PFS and OS compared with everolimus in Phase 3 Study XL184-308 in previously treated RCC patients (METEOR; Choueiri et al [N Engl J Med] 2015, Choueiri et al [Lancet Oncol] 2016) and in PFS compared with sunitinib in Phase 2 Study A031203 in treatment-naïve patients (CABOSUN; Choueiri et al [Ann Oncol] 2017, Choueiri et al [Eur J Cancer] 2018).

Immunotherapies have also expanded treatment options in RCC: the combination of nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA4 antibody) is indicated for treatment-naïve RCC patients while single-agent nivolumab is the only ICI indicated for the treatment of advanced RCC after prior anti-angiogenic therapy (Opdivo US PI and SmPC; NCCN V3.2018). Recently, clinical data from a randomized Phase 3 trial (CheckMate 214, Motzer et al 2018) have led to the approval in the US and other regions of nivolumab in combination with ipilimumab for treatment of previously untreated patients with intermediate- and poor-risk per IMDC criteria.

Preclinical studies (Kwilas et al 2014, Song et al 2015, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in patients with UC (Apolo et al 2014) suggest that cabozantinib promotes an immune-permissive environment, which might present an opportunity for synergistic effects from combination treatment with ICIs independent of tumor PD-L1 expression. In an ongoing Phase 1 study, the combination of cabozantinib with nivolumab and ipilimumab is being evaluated in subjects with previously treated advanced genitourinary cancers including UC and RCC (Apolo et al [Ann Oncol] 2016, Nadal et al 2017, Nadal et al 2018). In the dose escalation stage of the study, no DLTs were

reported for the cabozantinib and nivolumab combination (doublet) or the cabozantinib and nivolumab + ipilimumab (triplet) combination. Data are available for a total of 78 subjects enrolled in this trial, including 14 subjects with RCC. The ORR for 13 RCC subjects evaluable for response for either the doublet or triplet combination was 54% (7 responders of 13 subjects). The remainder of RCC subjects evaluable for response (6 of 13) had SD reported as their best response to date. There was a pronounced effect on PFS and OS: median PFS in these RCC subjects was 18.4 months (95% CI 6.4, 18.4) and the median OS was not reached. The triplet regimen was found to be tolerable and the available safety profile in this study reflects the established profile of cabozantinib and nivolumab + ipilimumab. There were no Grade 5 AEs.

Based on the encouraging clinical experience in the Phase 1 study, the current Phase 3 trial evaluates the safety and efficacy of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in subjects with locally advanced or metastatic RCC of intermediate or poor risk (as defined by IMDC criteria). The selection of the intermediate- and poor-risk population for the current study is based on results from the CheckMate 214 study, which did not show a clinical benefit for the nivolumab + ipilimumab combination relative to sunitinib in the IMDC favorable-risk subgroup (Motzer et al 2018).

The safety profile of each of the constituents of the triplet combination is well defined and the triplet combination has been studied in previous clinical trials. Dose management guidelines are included in the current study protocol for the most important risks (Section 6.6).

Study inclusion/exclusion criteria were designed to prevent subjects at a heightened safety risk from entering the study. The protocol provides guidance to investigators for the management of important AEs that are associated with cabozantinib (Section 6.6.2) and nivolumab and ipilimumab (Section 6.6.3). A pattern of immune-related AEs (irAEs) has been defined, for which management algorithms have been developed (Appendix E): most high-grade events are manageable with the use of corticosteroids or hormone replacement therapies as instructed in these algorithms. Frequent safety assessments including laboratory assessments allow identification and early intervention of potential AEs due to study treatment.

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. IDMC members will be selected for their expertise in conducting studies in oncology. Additionally, the Sponsor's Safety Committee will monitor the blinded safety of the study on a regular basis.

1.8.1 Summary of Benefits and Risks

Cabozantinib and the combination of nivolumab and ipilimumab have each demonstrated clinical activity in previously untreated intermediate- and poor-risk RCC patients, and cabozantinib in combination with nivolumab has demonstrated activity across all risk groups. In addition, preliminary clinical data suggest that cabozantinib in combination with nivolumab and ipilimumab exhibits clinical activity. Therefore, based on preclinical observations, the demonstrated clinical activity of nivolumab and ipilimumab and of cabozantinib in this patient population, and the known safety profiles of these agents, the potential benefits of evaluating these agents outweigh the potential risks.

1.9 Study Conduct

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines and also consistent with the most recent accepted version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel for whom sanctions have been invoked or there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment, etc).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objective of this study is to evaluate the efficacy and safety of the combination of cabozantinib with nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in previously untreated subjects with intermediate- and poor-risk advanced or metastatic RCC.

2.2 Endpoints

Primary Efficacy Endpoint:

- Duration of PFS, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), by Blinded Independent Radiology Committee (BIRC)

Secondary Efficacy Endpoint:

- Duration of OS

Additional Endpoints:

- ORR per RECIST 1.1 by BIRC
- PFS and ORR per RECIST 1.1 by BIRC according to PD-L1 status
- PFS and ORR per RECIST 1.1 as assessed by the Investigator
- Duration of radiographic response as assessed by the Investigator and by BIRC
- Safety through the evaluation of AEs, including irAEs, and other safety assessments.
- Pharmacokinetics (PK) of cabozantinib given in combination with nivolumab and ipilimumab
- Immunogenicity of nivolumab and ipilimumab given in combination with cabozantinib
- Correlation of biomarker analyses with clinical outcomes
- Health-related quality of life (HRQoL) as assessed by the EuroQol Health questionnaire instruments (EQ-5D-5L)
- Health care resource utilization

3 STUDY DESIGN

3.1 Study Sites

This study will be conducted at approximately 180 sites.

3.2 Estimated Study Dates and Duration of Subject Participation

It is estimated that 21 months will be required to randomize 840 subjects. The number of events required for the primary analysis of PFS (249 events among the first 440 subjects randomized) is expected to be observed approximately 23 months after the first subject is randomized. The number of events required for the final analysis for the secondary endpoint of OS (433 events among 840 subjects) is expected to be observed approximately 69 months after the first subject is randomized. The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active. The estimates for the timing of event-driven analyses do not include the additional months required for event ascertainment, data quality review, data analysis and interpretation.

It is estimated that subjects will participate for an average of 12-18 months on study treatment. Some study assessments continue periodically after study treatment is discontinued, and subjects will be followed until death, withdrawal of consent, or Sponsor decision to no longer collect these data.

3.3 Overview of Study Design

This is a Phase 3 multicenter, randomized, double-blind, controlled trial of cabozantinib with nivolumab and ipilimumab vs nivolumab and ipilimumab in subjects with intermediate or poor risk advanced or metastatic RCC not previously treated with systemic therapy. The primary efficacy endpoint is BIRC-determined PFS. Cabozantinib-matched placebo will be given in combination with nivolumab and ipilimumab in the control arm to mask (blind) the study treatment. Approximately 840 eligible subjects will be randomized to receive study treatment as described in Figure 3-1 and Section 3.4.

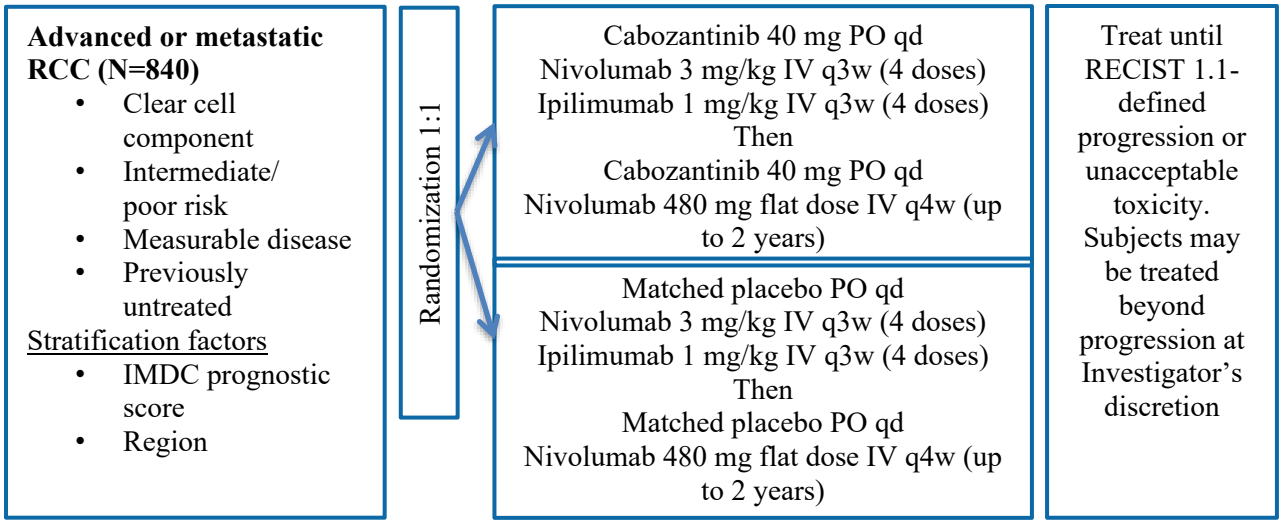
The study was originally designed to enroll 676 subjects; the sample size was increased to accommodate new, external data about the expected median overall survival in the control arm (see Section 9.5).

The PITT population may be expanded by 25% from the first 440 to the first 550 randomized if a review of accumulating PFS events suggests that the 249 events required for the analysis will not

be reached due to censoring caused by a higher than expected study drop-out or non-compliance stemming from the COVID-19 pandemic.

Special accommodations during the global COVID-19 pandemic are described in Appendix K.

Figure 3-1: XL184-313 Study Schema



IMDC, international metastatic renal cell carcinoma database consortium; IV, intravenous; PO, oral administration; qd, once daily; q3(4)w once every 3(4) weeks; RECIST, response evaluation criteria in solid tumors; RCC, renal cell carcinoma

Each subject's course of treatment will consist of the following periods:

Pre-Treatment Period: Potential subjects will be screened to determine whether they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive either cabozantinib in combination with nivolumab and ipilimumab or placebo in combination with nivolumab and ipilimumab. Details about the investigational regimens are provided in Section 6.

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for subsequent systemic anti-cancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.6). Treatment may continue after radiographic progression per RECIST 1.1 as long as the Investigator believes that the subject is still receiving clinical benefit from study

treatment and that the potential benefit of continuing study treatment outweighs potential risks (Section 5.7.6.2).

Transition to Unblinded Treatment: The study may transition to unblinded treatment at the discretion of the Sponsor and upon any necessary discussions with regulatory authorities after analyses of PFS and OS have been performed. If the study is declared futile or the null hypothesis for the primary endpoint of PFS is not rejected (negative study), the study will be unblinded and investigators and subjects will be notified. If the null hypothesis for the primary endpoint of PFS is rejected (positive study), the study will not be unblinded until the null hypothesis for the secondary endpoint of OS is rejected or the final analysis of OS is performed.

Once the study transitions to unblinded treatment, investigators and subjects will be notified of the randomized treatment assignment to allow for appropriate treatment decisions. Protocol procedures and assessments will continue without change.

Post-Treatment Period: Subjects who discontinue from study treatment (including subjects in the Maintenance Phase [below]) will return to the site for two follow-up visits for safety assessments. The first Post-Treatment Follow-up Visit (FU-1) for safety is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the decision to permanently discontinue study treatment or the last dose of study treatment). A second follow-up visit (FU-2) will be conducted approximately 100 (±14) days after the date of the decision to permanently discontinue study treatment. Radiographic tumor assessments and HRQOL assessments are to continue, regardless of whether study treatment is given, reduced, held or discontinued until a protocol-defined criterion for ending radiographic assessments is met. Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

In addition, subjects are to be contacted every 12 weeks (± 14 days) after the 100-day Post-Treatment Follow-Up Visit (FU-2) to assess survival status and document receipt of systemic nonprotocol anti-cancer therapy (NPACT). This will continue until the subject expires or the Sponsor decides to discontinue collection of these data. Further, coinciding with each analysis of OS, sites will be required to determine the survival status for all subjects not known to be deceased as of the data cutoff date for the analysis. This will require additional subject contacts outside the 12-week schedule. Every effort must be made to collect this protocol-specific information unless consent for non-interventional study assessments is withdrawn. Assessments of OS/NPACT are not required in the Maintenance Phase (below).

Study Completion: The study will be considered complete if any of the following criteria apply:

- futility analysis of PFS: the trial has been declared futile by the Sponsor, or
- primary analysis of PFS: null hypothesis is not rejected, or
- primary analysis of PFS: null hypothesis is rejected for PFS and the null hypothesis is rejected for OS (or the final planned analysis for OS has been conducted)

Maintenance Phase/Treatment After Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, and after treatment assignment has been unblinded, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes have been completed. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects on active study treatment will continue to receive study treatment until they meet the protocol-required criteria for treatment discontinuation. Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments. The nature and frequency of these assessments during the Maintenance phase are to be performed per institutional standard of care and guidance from the Sponsor as necessary (see Appendix B). It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of SAEs; certain AEs (including AESIs [whether serious or not], and AEs leading to dose modifications or treatment discontinuation); and other reportable events (drug-induced liver injury [DILI], pregnancy, and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.

The study clinical database will be closed upon initiation of the Maintenance Phase. Important safety information (noted above) collected in the Maintenance Phase will be captured in the safety database. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

End of Trial: End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

3.4 Treatment Groups and Randomization

After obtaining informed consent, the site representative will use the designated web-based interactive response technology (IRT) system to register a subject. The IRT will assign a unique subject number. When a subject has been deemed eligible at the study site, the site representative will use the IRT to randomize and enroll the subject into the study.

Eligible subjects will be randomly assigned in a 1:1 ratio to the following treatment arms:

- Experimental arm:
  Cabozantinib (40 mg oral, once daily [qd]) + nivolumab (3 mg/kg infusion, once every 3 weeks [q3w]) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses,
  followed by cabozantinib (40 mg oral qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.
- Control arm:
  Cabozantinib-matched placebo (oral, qd) + nivolumab (3 mg/kg infusion, q3w) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses,
  followed by cabozantinib-matched placebo (oral, qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.

Details about treatment regimens are provided in Section 6.

Randomization will be stratified by the following factors established at screening:

- IMDC prognostic score (1-2 risk factors [intermediate] vs 3-6 risk factors [poor])
- Region ([US or Canada or Europe or Australia or New Zealand] vs [Latin America or Asia])

The IMDC risk factors are (Heng et al 2009):

- Karnofsky performance status (KPS) < 80%
- Less than 1 year from initial RCC diagnosis (including original localized disease if applicable) to systemic treatment
- Hemoglobin < lower limit of normal (LLN)
- Corrected calcium > 10 mg/dL
- Absolute neutrophil count (ANC) > upper limit of normal (ULN)
- Platelet count > ULN

The most recent evaluations used to establish eligibility must be used to determine the risk factor category for stratification. Results from the central laboratory should be used for these purposes whenever possible. Local laboratory results for stratification will be allowed in instances where a central laboratory result has not been obtained and would delay randomization approval, or for laboratory values that are required to be repeated closer to randomization. Results from local laboratory assessments used to determine the appropriate stratification values are to be documented in source materials and carefully reviewed by site personnel before entry into the IRT for randomization and sent to the local laboratory management vendor of the study.

Randomization should occur as close as possible to the planned start of treatment (ie, within 3 days). Subjects are defined as enrolled in the study if randomized. Changes to stratification values entered in the IRT will not be performed after randomization. Randomization will not be voided except under very rare circumstances and with Sponsor approval. Subjects who sign consent, are assigned a subject identifier, and are screened (to any degree, including rescreening) but never randomized are deemed permanent screen failures.

3.5 Study Blinding

3.5.1 Blinding of Study Treatments

The cabozantinib-matched placebo will be given in combination with nivolumab and ipilimumab in the control arm to blind (mask) study treatment.

Study treatment assignment will be unknown to the subjects, investigators, study centers, Sponsor, and any contract research organization (CRO) affiliated with the study other than those authorized to access treatment assignment for regulatory safety reporting and submission processes (see Section 8.2.2), IRT administration, and drug supply management.

Cabozantinib-matched placebo will be packaged and color-, size-, and shape-matched to be indistinguishable from cabozantinib (Section 6.1).

3.5.2 Unblinding Procedure for Individual Subjects

Blinding of oral study treatment is critical to the integrity of this clinical study and therefore if a subject's treatment assignment is disclosed to the study site the subject will have all study treatment discontinued. In the event of a medical emergency, the treating physician may decide that knowledge of the investigational product is critical to the subject's management of that emergency. In this rare situation, the treating physician may access the treatment information for this subject through the IRT system. The blind should only be broken for the specific subject in question and, before breaking the blind of an individual subject's study treatment, the

Investigator should have determined that the information will alter the subject's immediate medical management. In the vast majority of cases, AEs may be properly managed without the need for unblinding (see Section 6.6). An unblinded notification including the subject ID, treatment arm, and date of unblinding will be provided to the Investigator.

3.6 Treatment Discontinuation and Study Withdrawals

Details for handling treatment discontinuation and study withdrawal are discussed in Sections 3.6.1 and 3.6.2, respectively.

If a subject requests to discontinue study treatment and/or withdraws study consent, the Investigator must establish the specific nature of the subject's request.

The subject's decisions for each individual component of study treatment (there may be more than one decision over time) must be recorded in source documents and transcribed to study case report forms (CRFs).

3.6.1 Treatment Discontinuation

Subjects will receive study treatment until treatment discontinuation for any of the reasons listed below. Subjects may discontinue study treatment and assessments or withdraw their consent to participate in the study at any time without prejudice. If a subject discontinues all study treatment, the reason will be documented in source documents and all study treatment will be stopped. The investigator may also discontinue a subject from all study treatment if in his or her clinical judgment it is in the best interest of the subject or if the subject cannot comply with the protocol. In addition, the Investigator will also discontinue a subject from study treatment upon the Sponsor's request or if the Sponsor chooses to terminate the study.

The following are possible reasons for discontinuation of all study treatment:

- Subject no longer experiences clinical benefit as determined by the Investigator (eg, disease progression [PD] and/or clinical deterioration attributable to PD where either is unlikely to reverse with continued study treatment and/or supportive care).
- Unacceptable side effects the Investigator feels may be due to study treatment. Continuation of one component of the combination study treatment while discontinuing the other will be allowed. The Investigator is encouraged to discuss such circumstances with the Sponsor.
- The investigator feels it is not in the best interest of the subject to continue on study.

- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention.
- Necessity for treatment with non-protocol systemic anti-cancer therapy.
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment related AEs unless approved by the Sponsor. (Note: temporary interruptions of study treatment for greater than 12 weeks due to the effects of COVID-19 and unrelated to AEs are described in Appendix K.)
- Refusal of sexually active fertile subjects to use highly effective methods of contraception (defined in Appendix D).
- Female subjects who become pregnant.
- Request by the Sponsor
- Unblinding of study treatment by the Investigator (prior to unblinding of study treatment for all subjects)
- Subject request to discontinue all study treatments (with or without concurrent withdrawal of informed consent).
- Significant noncompliance with the protocol schedule in the opinion of the Investigator or the Sponsor.
- Subject is determined to have been randomized to receive placebo following study-wide unblinding

In addition, specific criteria for discontinuation of cabozantinib are provided in Section 6.6.2 and for discontinuation of nivolumab/ipilimumab are provided in Section 6.6.3.2. The maximum treatment period for nivolumab/ipilimumab is specified in Section 3.4.

To ensure timely Sponsor notification of study treatment discontinuations, site personnel are to promptly record treatment discontinuations in the study IRT. The reason for study treatment discontinuation must be recorded in source documents and CRFs. If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter requesting contact with the clinic should be sent to the subject (or the subject's legal guardian).

For subjects who discontinue study treatment, every effort must be made to undertake protocol-specified follow up procedures including end of treatment assessments, survival

follow-up, and documentation of subsequent anti-cancer treatment(s) unless consent for non-interventional study assessments is also withdrawn.

If a subject is discontinued from study treatment because of an AE (including AESI; Table 8-1) considered to be related to study treatment, the event must be followed until resolution or determination by the Investigator that the event has become stable or irreversible.

3.6.2 Study Withdrawal

Upon discontinuation of study treatment, at any time without prejudice, subjects may:

- Continue study interventions (eg, examination, blood and tissue sampling radiographic assessments, questionnaires) and non-interventional study assessments (eg, medical record review, survival contacts), or
- Withdraw their consent for study interventions but continue non-interventional study assessments, or
- Withdraw their consent for both study interventions and non-interventional study assessments.

Reasons for study withdrawal will be recorded in the source documents and CRFs. As applicable, no further study procedures or assessments will be performed or study data collected. For subjects who withdraw consent, determination of survival status from public records such as government vital statistics or obituaries will be performed as allowed by local regulations. Subjects who withdraw from the study will not be replaced.

3.6.3 Study Completion

The study will be considered complete if any of the following criteria apply:

- futility analysis of PFS: the trial has been declared futile by the Sponsor, or
- primary analysis of PFS: null hypothesis is not rejected, or
- primary analysis of PFS: null hypothesis is rejected for PFS and the null hypothesis is rejected for OS (or the final planned analysis for OS has been conducted).

3.6.4 End of Trial

End of trial is defined as the last scheduled visit or scheduled procedure for the last subject (including Maintenance Phase assessments).

4 STUDY POPULATION

4.1 Target Population

This study will enroll subjects with previously untreated intermediate- and poor-risk advanced or metastatic RCC. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to safeguard the integrity of the study results. It is imperative that subjects fully meet all inclusion criteria and none of the exclusion criteria. The Sponsor will not grant waivers to study eligibility criteria.

4.2 Inclusion Criteria

1. Histologically confirmed advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) renal cell carcinoma with a clear-cell component, including subjects who also have a sarcomatoid feature.
2. Intermediate- or poor-risk RCC as defined by IMDC criteria (Section 3.4)
3. Measurable disease per RECIST 1.1 as determined by the Investigator. Measurable disease must be outside the radiation field if radiation therapy was previously administered.
4. Shipment of archival tumor tissue (unstained slides or paraffin block) to the study central laboratory prior to randomization. The tumor tissue can be obtained from any organ except brain or bone and must have been biopsied no more than 2 years prior to the date of informed consent. Alternatively, a fresh tumor sample must be obtained and shipped to the study central laboratory prior to randomization if archival tumor tissue is unavailable or inadequate.
5. Recovery to baseline or ≤ Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. Examples of exceptions are subjects with Grade 2 neuropathy or alopecia who are allowed for trial participation.
6. Age eighteen years or meeting country definition of adult, whichever is older, on the day of consent.
7. Karnofsky Performance Status (KPS) ≥70%.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization:
    a. Absolute neutrophil count (ANC) ≥ 1500/µL (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection.
    b. Criterion intentionally left blank
    c. Platelets ≥ 100,000/µL (≥ 100 GI/L) without transfusion within 2 weeks before screening laboratory sample collection.

d. Hemoglobin ≥ 8 g/dL (≥ 80 g/L) without transfusion within 1 week before screening laboratory sample collection and no clinical evidence of bleeding.

e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.

f. Total bilirubin ≤ 1.5 × ULN (with the exception that total bilirubin for subjects with Gilbert's disease ≤ 3 × ULN).

g. Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation (see Table 5-3 for Cockcroft-Gault formula).

h. Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h urine protein ≤ 1 g.

9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessments except those procedures performed as standard of care within the screening window.

10. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception (defined in Appendix D) during the course of the study and for 5 months for women, and 7 months for men, after the last dose of study treatment. A barrier contraceptive method (eg, condom) is also required.

11. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman > 45 years-of-age in the absence of other biological or physiological causes. In addition, females < 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

4.3 Exclusion Criteria

1. Prior systemic anticancer therapy for unresectable locally advanced or metastatic RCC including investigational agents.
Note: One prior systemic adjuvant therapy is allowed for completely resected RCC and if recurrence occurred at least 6 months after the last dose of adjuvant therapy.
Note: Adjuvant therapy with a PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor is not permitted.

2. Radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.

3. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or radiosurgery and stable for at least 4 weeks prior to

randomization after radiotherapy or at least 4 weeks prior to randomization after major surgery (eg, removal or biopsy of brain metastasis). Subjects who are neurologically symptomatic as a result of their CNS disease, or are receiving systemic corticosteroid treatment (prednisone equivalent > 10 mg/day) at the planned time of randomization are not eligible.

4. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).

    a. Allowed anticoagulants are:

        i. Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)

        ii. Therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor

    Note: Subjects who switch from an oral anticoagulant to LMWH are allowed if the oral anticoagulant was stopped ≥ 5 half-lives of the oral anticoagulant prior to planned randomization date.

5. Administration of a live, attenuated vaccine within 30 days prior to randomization. The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.

6. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders:

        i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, Torsades de pointes).

        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.

        iii. Stroke, transient ischemic attack (TIA), myocardial infarction, or other symptomatic ischemic event or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism [DVT/PE]) within 6 months before randomization.

        Note: Subjects with a diagnosis of DVT within 6 months are allowed if asymptomatic and stable at screening and treated with LMWH for at least 1 week before randomization.

        Note: Non-symptomatic white matter disease in the brain is acceptable.

    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.

ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra-abdominal abscess must be confirmed prior to randomization.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:

i. Autoimmune disease that has been symptomatic or required treatment within the past two years from the date of randomization.

Note: Patients with a history of Crohn's disease or ulcerative colitis are always excluded
Note: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Note: Inhaled, intranasal, intra-articular, or topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.

iii. Active infection requiring systemic treatment. Acute or chronic hepatitis B or C infection, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or known positive test for tuberculosis infection where there is clinical or radiographic evidence of active mycobacterial infection.

iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomograph (CT) scan

v. Serious non-healing wound/ulcer/bone fracture.

vi. Malabsorption syndrome.

vii. Uncompensated/symptomatic hypothyroidism.

viii. Moderate to severe hepatic impairment (Child-Pugh B or C) (Appendix J).

ix. Requirement for hemodialysis or peritoneal dialysis.

x. History of solid organ or allogeneic stem cell transplant.

xi. Known history of COVID-19 unless the subject has clinically recovered from the disease at least 30 days prior to randomization.

7. Major surgery (eg, nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks prior to randomization. Minor surgeries within 10 days prior to randomization. Subjects must have complete wound healing from major or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
8. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before randomization. Furthermore, subjects with a history of additional risk factors for torsades de pointes (eg, long QT syndrome) are also excluded.

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility
9. History of neuropsychiatric disorder likely to interfere with ability to comply with protocol requirements or give informed consent.
10. Pregnant or breastfeeding females.
11. Inability to swallow tablets or unwillingness or inability to receive IV administration.
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe infusion-related reactions to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.
13. Any other active malignancy at time of randomization or diagnosis of another malignancy within 3 years prior to randomization that requires active treatment, 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.

5 STUDY ASSESSMENTS AND PROCEDURES

This protocol generally presents scheduled timelines for study procedures by abbreviated references to week (W) and day (D) (eg, W1D1, W3D1 etc.) relative to the date of the first dose of study treatment (defined as W1D1). Study W1D1 should occur within 3 days of the date of randomization (which will be defined as W1D1 for subjects randomized who never receive study treatment).

All assessments for safety and HRQOL assessments will be scheduled based on W1D1.

Unscheduled visits for safety evaluations are allowed at any time and required in circumstances described herein.

All assessments for efficacy (CT or magnetic resonance imaging [MRI], bone scans) and HRQOL will be scheduled based on the date of randomization.

See Appendix A for the schedule of assessments. Special accommodations during the global COVID-19 pandemic are described in Appendix K.

5.1 Pre-Treatment Period

Informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research. However, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies. Informed consent may be obtained greater than 28 days before randomization. At informed consent a study site representative will use the web-based IRT to register subjects. The IRT will assign a unique subject identifier; subject identifiers are not to be re-assigned if a subject is determined to be ineligible, and subjects are to maintain their original identifier if re-screening is required or if the subject experiences a change in study site or investigator.

To determine subject eligibility as stipulated in Section 4, subjects will undergo required screening evaluations as outlined in Appendix A and described in Section 5.7. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise stated (eg, certain laboratory values must be obtained closer to randomization). Eligibility criteria based on laboratory values should be based on central laboratory results whenever possible with the exception of serum pregnancy test for females of childbearing potential and urinalysis, which will be performed at the local laboratory. Local laboratory results can be used in lieu of central laboratory results in instances when a central laboratory result has not been obtained in time and would delay randomization approval or for laboratory tests that are required to be repeated closer

to randomization. Study eligibility is based on a subject meeting all of the study inclusion criteria and none of the exclusion criteria at screening.

Information to be collected on screen failures: a subject who signs informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. Data on the following will be collected for all screen failures:

- Informed consent information
- Failed inclusion/exclusion criteria
- Demographics
- Serious adverse events (SAEs)

5.2 Treatment Period

Subjects eligible after completing all screening evaluations will be randomly assigned in a 1:1 fashion (Section 3.4) to receive either cabozantinib in combination with nivolumab and ipilimumab or cabozantinib-matched placebo in combination with nivolumab and ipilimumab (Section 6.1.1). Subjects should receive their first dose of study treatment within 3 days after randomization.

While the subject is receiving study treatment, the subject's clinical status is to be evaluated by an Investigator at each clinic visit to confirm that the subject is suitable for continuing study treatment and to make timely decisions regarding any reduction (cabozantinib/placebo only), interruption, or restarting of study treatment. Clinical laboratory results from samples obtained during clinic visits and tumor assessments from imaging visits are to be reviewed by an Investigator

Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for subsequent systemic anti-cancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.6). Study treatment may continue after radiographic progression per RECIST 1.1 as long as the Investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks (Section 5.7.6.2). Crossover between treatment arms will not be allowed.

Study completion is defined in Section 3.6.3.

Safety will be assessed on the date of the first dose (W1D1) and every 3 weeks (W4D1, W7D1, W10D1), and then every 4 weeks thereafter (W14D1, W18D1, W22D1 etc). Additional evaluations of hematology, serum chemistry, and urinalysis will be performed at W3D1, W6D1, W9D1, and W12D1. Safety follow-up visits will be performed 30 (+14) days (FU-1 visit) and approximately 100 (±14) days (FU-2 visit) after the date of the decision to permanently discontinue study treatment (see Section 5.4). All post-randomization safety laboratory tests may be assessed by local laboratories.

If study treatment is held due to AEs, investigators should perform additional safety assessments weekly (or more frequently as clinically indicated).

Radiographic tumor assessments should be performed as described in Section 5.7.6, and HRQOL assessments should be performed as described in Section 5.7.7. The schedule of assessments should be maintained regardless of whether study treatment is given, reduced, held or discontinued.

In accordance with the ITT principle, HRQOL, radiographic tumor assessments, and survival follow-up are to be performed per protocol even for subjects randomized who never receive study treatment. For such subjects, W1D1 is defined as the date of randomization.

5.3 Transition to Unblinded Treatment

The study may transition to unblinded treatment at the discretion of the Sponsor and upon any necessary discussions with regulatory authorities after analyses of PFS and OS have been performed. If the study is declared futile or the null hypothesis for the primary endpoint of PFS is not rejected (negative study), the study will be unblinded and investigators and subjects will be notified. If the null hypothesis for the primary endpoint of PFS is rejected (positive study), the study will not be unblinded until the null hypothesis for the secondary endpoint of OS is rejected or the final analysis of OS is performed.

Once the study transitions to unblinded treatment, investigators and subjects will be notified of the randomized treatment assignment to allow for appropriate treatment decisions. Protocol procedures and assessments will continue without change.

5.4 Post-Treatment Period

Subjects who discontinue from study treatment (including subjects in the Maintenance Phase [below]) will return to the site for two follow-up visits for safety assessments. The first follow-up

visit (FU-1 visit) will occur 30 (+14) days and the second follow-up visit (FU-2) will occur 100 (±14 days) after the date of the decision to discontinue study treatment. Refer to Appendix A for a description of all assessments for the Post-Treatment Follow-Up Visits. Further details on AE follow up and data collection requirements are available in Appendix H.

Adverse events are to be documented and/or followed as described in Section 8.3.

Following treatment discontinuation each subject will continue to be followed for survival. The investigator (or designee) will make contact with the subject every 12 weeks (± 14 days) after the second follow-up visit (FU-2) until the subject expires, withdraws consent for such contacts, or the Sponsor decides to cease collecting these data for the study.

At each contact, the Investigator (or designee) will determine whether the subject died, and if so, record the date and cause of death as best can be determined. All efforts must be undertaken by the study sites to determine the date of death (or date subject last known alive at the time of a data cutoff). This may include, but not necessarily be limited to, telephone contacts, communication at study visits, registered letters, and reviews of local obituaries and government death records. Receipt of systemic NPACT will also be collected during the Post-Treatment Period. If a subject is lost to follow-up, multiple attempts to contact the study subject or designee must be documented in the subject records.

HRQOL outcomes and radiographic tumor assessments will be collected regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment as described in Section 5.7.6. Consequently, these assessments may be required in the Post-Treatment Period for some subjects.

5.5 Maintenance Phase/Treatment After Study Completion

The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after the study objectives have been completed (Study Completion, see Section 3.6.3). When sufficient data have been collected to adequately evaluate all study endpoints, and after treatment assignment has been unblinded, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established, and data analyses required for regulatory purposes have been completed. The Sponsor is to notify the sites if or when the study will enter

the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase, subjects on active study treatment will continue to receive study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.6.1). Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments (Appendix B). The nature and frequency of these assessments are to be performed per institutional standard of care and guidance from the Sponsor as necessary. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs, and other reportable events (DILI, pregnancy, and medication errors with sequelae) is to continue per protocol (Section 8.2).

Further, the following AEs, whether serious or not, are to be reported using the same process as for reporting SAEs described in the protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse events of special interest (AESIs)
- Adverse events, whether serious or not, leading to study treatment discontinuation
- Adverse events, whether serious or not, leading to study treatment dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)

Study drug accountability is to continue as described in Section 6.5.

Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

5.6 Unscheduled Visits or Assessments

If the Investigator determines that a subject should be monitored more frequently or with additional laboratory parameters assessments than indicated by the protocol-defined visit schedule, unscheduled visits or assessments are permitted. The laboratory assessments should be done by the central laboratory; however, if the results are needed immediately (eg, for AE management), they may be done by the local laboratory and the results forwarded to the management vendor for handling of local laboratory data. In such instances, a sample for central laboratory analysis should also be collected. If study treatment is held, the study site should perform unscheduled visits weekly (or more frequently) as clinically indicated during the

intervening time between the last dose and the time drug is restarted to monitor subject safety and appropriateness for re-treatment.

5.7 Procedure details

This section describes evaluations to be performed and items to be recorded or available on source documents. Data from some required evaluations may not be collected on study case report forms (CRFs; see Section 16.4).

5.7.1 Demographics, Baseline Characteristics, Medical and Cancer History

Demographics at screening will include age at informed consent, medical and cancer history, surgical history, radiation therapy history, and systemic anti-cancer treatment history including names of agents and administration dates. To ensure subject privacy, date of birth and subject initials will not be collected by the Sponsor.

The study will enroll RCC subjects of intermediate- or poor-risk per IMDC criteria. The following IMDC risk factors (Heng et al 2009) should be scored per Table 5-1:

- Karnofsky performance status < 80%
- Less than 1 year from initial RCC diagnosis (including original localized disease if applicable) to systemic treatment
- Hemoglobin < LLN
- Corrected calcium > 10 mg/dL
- Absolute neutrophil count > ULN
- Platelet count > ULN

The most-recent evaluations used to establish eligibility must be used to determine the risk factor category for stratification. Results from assessments used to determine the appropriate stratification values are to be documented in source materials and carefully reviewed by site personnel before entry into the IRT for randomization.

Table 5-1: IMDC Prognostic Score

Prognosis	Number of risk factors
Favorable	0
Intermediate	1 or 2
Poor	3 or more

Source: Heng et al 2009

5.7.2 Physical Examination

Physical examinations will include height (screening visit only), weight, performance status, and an assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory system, cardiovascular system, GI system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. Symptom-directed physical examination will be conducted on W1D1 before first dose of study treatment and after randomization. Any ongoing/intercurrent condition prior to first dose must be recorded as medical history. Significant new findings that begin or worsen after first dose must be recorded as AEs.

The KPS score of the subject will be assessed at screening and each scheduled safety assessment starting on W1D1. A table of KPS criteria is included in Appendix C for reference.

Refer to Appendix A for the schedule of physical examination and KPS assessments.

5.7.3 Vital Signs

Vital signs including approximately 5-minute sitting BP, pulse, respiration rate, and temperature will be assessed according to the schedule in Appendix A.

On study treatment infusion days, vital signs should be assessed within 60 minutes prior to initiation of the infusion, and further vital sign assessment should be performed during and after the infusion as clinically indicated.

5.7.4 Electrocardiograms

At screening and during the study, single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine the corrected QT interval calculated by the Fridericia formula (QTcF). A QTcF ≤ 500 ms per ECG within 14 days before randomization is required to demonstrate eligibility for study treatment. If at any time a single ECG shows a QTcF with an absolute value > 500 ms or an increase in the QTcF of at least 60 ms from baseline, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used as the value assessed (see Section 6.6.2.1.15).

ECGs will be performed at the time points indicated in Appendix A.

Abnormalities in the ECG that lead to a change in subject management (eg, dose reduced or interrupted, treatment discontinued, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this

study and will be deemed AEs. If values meet criteria defining them as serious, they must be reported as SAEs (Section 8.2).

The Fridericia formula is depicted below for calculation of the QTcF value.

$$QTcF = \frac{QT}{RR^{1/3}}$$

QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate)

5.7.5 Safety Laboratory Assessments

Laboratory analytes that will be measured for this study are listed in Table 5-2.

The schedule for laboratory assessments is provided in Appendix A. Laboratory tests to establish eligibility must be done within 14 days before randomization unless otherwise stated (Appendix A). Laboratory values essential for eligibility determination should be obtained from the central laboratory whenever possible with the exception of serum pregnancy test for females of childbearing potential and urinalysis, which will be performed at the local laboratory. Local laboratory results can be used in lieu of central laboratory results in instances when a central laboratory result has not been obtained in time and would delay randomization approval and for laboratory tests that are required to be repeated closer to randomization or within 72 hours of checkpoint inhibitor infusion.

The following is a list of criteria for conducting safety laboratory assessments:

- Central laboratory assessment is required for pharmacokinetics (PK) and immunogenicity measurements;
- Local laboratory assessment is required for:
    - 24-hour urine protein tests (if performed in addition to or in lieu of urine protein/creatinine ratio), with results forwarded to the local lab management vendor;
    - HIV testing, if mandated by local institution guidance;
    - Urinalysis, microscopic urine examination (if needed), serum/urine pregnancy (for females of childbearing potential). Results or status from these tests will be

recorded on CRFs but will not be submitted to the study local laboratory management vendor.

- Labs required within 72 hours of infusions of nivolumab and ipilimumab, ie, hematology, serum chemistry and urinalysis, may be obtained through the local lab.

Specific laboratory test information:

- To confirm suitability for treatment, all laboratory tests (except for pregnancy test) must be performed within 14 days prior to administering the first dose of study treatment. Serum chemistry tests will include corrected calcium. These assessments do not need to be performed on W1D1 unless the subjects' clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration) since the most recent assessment performed to establish eligibility and suitability for study treatment, or if required by local institution guidance. If any of these tests are performed on W1D1, the results must be available to and reviewed by the Investigator prior to any treatment being administered. For all subsequent treatments, serum chemistry, hematology, and urinalysis laboratory samples must be collected within 72 hours and the results reviewed before any study treatment infusion is administered on study.
- A serum pregnancy test (for females of childbearing potential) must be repeated before dosing on W1D1 unless a pregnancy evaluation was done during screening within 7 days prior to W1D1.
- Follicle stimulating hormone (FSH) is required for women under the age of 55 years to confirm menopause during the screening period.
- Hepatitis B viral infection status is determined by assessment of hepatitis B surface antigen (HBsAg).
- Hepatitis C viral infection status is guided by HCV antibody status; if positive, then a reflex test for HCV RNA determines eligibility.
- Thyroid function assessment must comprise TSH and free T4 evaluations. Free T4 is required at screening and is required subsequently only if the TSH is out of range.

Table 5-2: Laboratory Panels

Central or Local Laboratory

If performed by local laboratory, submit results to study local laboratory management vendor

Hematology

- White blood cell (WBC) count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)
- hematocrit
- platelet count
- red blood cell count
- hemoglobin

Coagulation

- prothrombin time (PT)/ International Normalized Ratio (INR)
- partial thromboplastin time (PTT)

Thyroid function

- thyroid-stimulating hormone (TSH)
- Free thyroxine (T4; required at screening; after screening only if TSH is outside normal range)

Other parameters

- Follicle stimulating hormone (FSH)[a]

Serum Chemistry

- albumin
- total alkaline phosphatase (ALP)
- amylase
- alanine amino transferase (ALT)
- aspartate amino transferase (AST)
- blood urea nitrogen (BUN)
- corrected calcium
- bicarbonate
- chloride
- creatinine
- γ-glutamyltranspeptidase (GGT)
- glucose
- lactate dehydrogenase (LDH)
- lipase
- magnesium
- phosphorus
- potassium
- sodium
- total bilirubin (including conjugated and unconjungated fractions)
- total protein

Virology

- hepatitis B surface antigen (HBsAg; screening)
- hepatitis C virus antibody (HCV Ab; HCV RNA reflex testing if antibody positive [screening])

Urine Chemistry

- Protein (spot urine; fully quantitative)
- Creatinine (spot urine; fully quantitative)
- Urine protein/creatinine ratio (UPCR; spot urine)

Local Laboratory Only

Submit only 24-hour urine protein test results to study local laboratory management vendor

Urinalysis

(Dipstick or Routine per Institutional Standard)

- pH
- specific gravity
- ketones
- protein
- glucose
- nitrite
- urobilinogen
- leukocyte esterase
- blood

Microscopic Urine Examination

- Perform at the discretion of the Investigator based on results or routine urinalysis or as clinically indicated

Urine Chemistry

- 24-hour urine protein: perform at the discretion of the Investigator based on increases in UPCR from routine assessments

Pregnancy Blood Test (prior to first dose)

- β-human chorionic gonadotropin (β-HCG)

Pregnancy Urine or Blood Test (after first dose of study treatment)

- β-human chorionic gonadotropin (β-HCG)

Virology

- HIV (if mandated locally [screening])

[a] For women under the age of 55 years to confirm menopause

Table 5-3: Estimation of the Creatinine Clearance by Cockcroft and Gault

Serum creatinine in conventional units (mg/dL) • Males: (140 – age) x weight (kg)/(serum creatinine × 72) • Females: [(140 – age) x weight (kg)/(serum creatinine × 72)] × 0.85
Serum creatinine in SI units (µmol/L) • Males: [(140 – age) x weight (kg)/(serum creatinine)] × 1.23 • Females: [(140 – age) x weight (kg)/(serum creatinine)] × 1.04

Abnormalities in any clinical laboratory test (including tests not required per protocol) that lead to a change in subject management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and should be reported as AEs. If laboratory values constitute part of an event that meets seriousness criteria, the event (with associated laboratory values) needs to be reported as an SAE (see Section 8.2).

5.7.6 Tumor Assessments

5.7.6.1 General

Radiographic response and PD will be determined using RECIST version 1.1 (Appendix F). For the purpose of determination of the radiographic study endpoints, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments will be promptly sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions. Sites will be provided with instructions for how images should be collected and submitted to the BIRC. Study staff shall ensure that no images contain personal data as defined by applicable local, regional, and international laws and regulations.

Radiographic tumor assessments will include the following:

1. **Chest / Abdomen / Pelvis (CAP):** CT of CAP or CT chest and MRI abdomen/pelvis will be performed in all subjects at screening (prior to randomization). The first tumor assessment after randomization should be performed at W10D1 (± 7 days). Subsequent tumor assessments should be performed every 8 weeks (± 7 days) through Week 50. Upon completion of 50 weeks on study, these assessments will be performed every 12 weeks (± 7

days). Additional imaging of potential disease sites should be performed whenever radiographic PD is suspected.

2. **Brain:** MRI (or CT) of the brain will be performed in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis (or if clinically indicated) following the same post-baseline frequency as the imaging for CAP. MRI is the preferred method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless MRI is contraindicated. (Note: in order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization after radiotherapy or major surgery [eg, removal or biopsy of brain metastasis].)

3. **Bone scans**: Technetium bone scans (TBS) should be performed at screening for all subjects. After randomization, bone scans will be performed in subjects with known bone metastases and otherwise as clinically indicated per standard of care. Any soft tissue lesions associated with identified bone lesions must be imaged by CT/MRI and assessed in alignment with the CAP assessments. Bone scan findings alone cannot be used for the determination of progression or response and need to be corroborated by CT or MRI (which will be used as the basis for RECIST evaluations).

The same imaging modalities used at screening are to be used for subsequent tumor assessments after randomization. If there is clinical concern regarding the administration of any contrast, then a non-contrast CAP imaging study is acceptable as a screening assessment if it clearly demonstrates measurable disease per RECIST 1.1 that can be followed without the need for contrast. If at a follow up imaging time point the use of contrast is prohibited (eg, due to acquired impaired renal function or contrast allergy) then the same modality should be used without contrast.

Tumor assessments should continue on the protocol-defined schedule, relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued.

Radiographic response and PD will be determined using RECIST 1.1. Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study treatment if the subject is tolerating it acceptably, repeat radiographic tumor imaging at the next scheduled time point, and delay determination of progression until the findings indicating radiographic progression are unequivocal. Radiographic progression determined by the

Investigator does not necessarily warrant discontinuation of tumor assessments or study treatment.

Radiographic tumor assessments are to continue until the following criteria are met:

- For subjects who discontinue study treatment upon determination of Investigator-assessed radiographic PD per RECIST 1.1, tumor assessments may cease.
- For subjects who discontinue study treatment before Investigator-assessed radiographic PD, tumor assessments are to continue per the protocol-defined schedule until Investigator-assessed radiographic PD per RECIST 1.1.
- For subjects who continue to receive study treatment after Investigator-assessed radiographic PD because of Investigator-assessed clinical benefit which outweighs the potential risks, tumor assessments are to continue per the protocol-defined schedule until study treatment is permanently discontinued.

Refer to Appendix A for the schedule for these assessments.

5.7.6.2 Confirmation of Tumor Response and Tumor Progression

For subjects with an overall response of PR or CR per RECIST 1.1 by investigator at a given time point, a repeat assessment is to be performed no fewer than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled tumor assessment.

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have tumor measurement outcomes confirmed after the initial PD criteria were met. This is to be performed no later than the next scheduled tumor assessment. After discussion with and agreement from the Sponsor, continuation of study treatment after confirmatory tumor imaging for PD is allowed for subjects who meet all the following criteria:

- Clinical benefit per investigator judgment
- ECOG performance status of 0 or 1
- Absence of unmanageable treatment-related AEs
- Tumor status does not require urgent alternative medical interventions (eg, central nervous system [CNS] metastases)

Subjects who are eligible to continue with study treatment must provide written informed consent .

Reasons for treatment discontinuation are provided in Section 3.6. For subjects who continue treatment after documentation of radiographic progression, regularly scheduled imaging will continue until treatment discontinuation.

5.7.6.3 Blinded Independent Radiology Committee (BIRC)

All radiological studies acquired at all scheduled time points and any additional (unscheduled) radiological images acquired for tumor lesion assessment must be sent to the BIRC, preferably in original Digital Imaging and Communications in Medicine (DICOM) format (as detailed in the Site-specific Imaging Core Manual). Electronic transfer of scan files (via FTP, HTTP, or similar means) is preferred, although transfer on physical media (such as DVDs or CDs) is acceptable. For digital media, each disk should contain one time point for one subject. The site is expected to maintain a copy of digital data for the retention period applicable to the protocol, GCPs, and federal, international and/or state legal and medical requirements. The Sponsor and or designee will retain the media for the life of the study.

The BIRC will evaluate prior radiation history for the purpose of valid identification of target lesions and will review all images per RECIST 1.1 in a central, blinded, and independent fashion.

5.7.7 Health-related Quality of Life Assessments

Health-related quality of life (HRQOL) assessments will be performed using the EuroQol Health questionnaire instruments EQ-5D-5L. This is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS) (Appendix I). The utility data generated from EQ-5D assessments are recommended for and commonly used in cost effectiveness analysis. The first assessment will be at Screening within 14 days prior to randomization. Assessment will be collected every 3 weeks after randomization until W10D1 and every 4 weeks thereafter. Subjects will continue completing questionnaires regardless of whether study treatment is given, reduced, held, or discontinued until the date of the last tumor imaging assessment or the study meets its primary endpoint. Consequently, these assessments may be required in the Post-Treatment Period for some subjects (Appendix A).

Subjects are to complete the questionnaires prior to each clinic visit. If a clinic visit is not possible, subjects should complete the questionnaires as per schedule and return it to the site either during the next visit or send it to the site by fax or postal mail. Ideally, study subjects should not receive any information about their most recent medical results prior to completing the questionnaires in order to ascertain that their reporting not be influenced by such information

when completing the questionnaires. At clinic visits, questionnaires should be carefully reviewed by the study staff at the site for completeness.

Subjects who are not compliant with completing the questionnaires should be reminded by the Investigator that these reports are an essential part of the study and timely completion is required.

Every effort should be made by the study site to retrieve all HRQOL questionnaires, including the assessment following radiographic progression or discontinuation of study treatment, and to keep them at the site as source documentation.

Translated copies of the EQ-5D-5L questionnaires, if required, and instructions for filling them out will be provided to each study site in a separate study manual.

Completed questionnaires and any unsolicited comments written by the subject should be reviewed and assessed by the Investigator for responses that could indicate potential (S)AEs. This assessment should be documented in the study source records.

Patient-reported outcomes cannot be provided by study personnel.

HRQOL assessments will no longer be collected for subjects if the study transitions to the Maintenance Phase.

5.7.8 Health Care Resource Utilization

Health care resource utilization parameters will be collected from randomization through the FU-2 visit. These include hospital admissions, emergency room visits, intensive care unit admissions, length of stay, surgeries, and transfusions.

These data will not be collected in the Maintenance Phase.

5.7.9 Pharmacokinetic Assessments

Blood samples for PK assessment will be obtained from all subjects in both study arms. Samples will be collected for plasma cabozantinib concentration measurement pre-dose on W1D1, W4D1, W7D1, W10D1, and W14D1. The results will be used to confirm exposure to cabozantinib and to further characterize the population PK and exposure-response relationships for cabozantinib in this population.

Serum concentrations of nivolumab and ipilimumab will be measured. Samples will be collected for serum nivolumab and ipilimumab concentration measurement predose on W1D1, W4D1,

W7D1, W10D1, W14D1, W26D1, FU-1 and FU-2 visits. The results would be used to confirm exposure to nivolumab and ipilimumab.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of PK sample collection and processing will be provided to the site in the laboratory/procedure manual.

Collection of PK samples may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

5.7.10 Immunogenicity Assessments

Blood samples will be obtained from all subjects in both study arms for immunogenicity assessment (anti-drug antibodies [ADA] for nivolumab and ipilimumab) by validated immunoassays predose on W1D1, W14D1, W26D1, and FU-1 and FU-2 visits. Samples will be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab if ADA testing is positive.

5.7.11 Biomarker Assessments

Blood and tissue samples will be obtained once consent is provided and shipped to central laboratory for analysis. Refer to Appendix A for the schedule for these assessments and to "Exelixis Laboratory Manual for PD/Biomarker Samples" for specific details.

Tumor tissue (most recent archival [ie, within 2 years prior to date of informed consent]) will be obtained during screening. PD-L1 expression (28-8 monoclonal antibody) by IHC of tumor material will be determined and results will be provided during the course of the study. If no archival tumor tissue is available, a fresh biopsy must be collected in order to be considered for study participation.

For assessment of PD-L1 expression, evaluation of at least 100 viable tumor cells is required. Positive staining is defined as ≥ 1% and negative staining is defined as <1% of cells that exhibit circumferential and/or partial linear plasma membrane staining at any intensity. High cytoplasmic staining can interfere with membrane scoring and will define as "indeterminate". Additionally, failure of PD-L1 staining due to suboptimal tissue sample integrity or assay failure will also be defined as "indeterminate".

An optional biopsy can be collected approximately 6 weeks post first dose of study treatment. Peripheral blood samples will be obtained pre-dose and on days as specified in the Schedule of Assessments.

Exploratory analyses may include, but may not be limited to, the following:

- PD-L1 and MET in tumor specimens for association with clinical outcomes
- T-cell infiltration and tumor gene expression (ie, mutational load assessment) in tumor specimens and blood for association with clinical outcome
- Circulating immune cells in peripheral blood (ie, lymphocyte subset analyses by flow cytometry)
- Plasma biomarkers (ie, cytokines/chemokines, VEGF, metabolome)
- Tumor whole-genome sequencing and gene expression analysis
- Cell and/or pharmacogenomic analyses (ie circulating tumor DNA [ctDNA])

Collection of biomarker samples (with the exception of PD-L1 assessments) may be halted early or sampling frequency may be reduced at the discretion of the Sponsor.

The required blood samples will be used to study plasma, serum, and cellular biomarkers. The most recent archival/fresh tumor biopsy and optional on-treatment tumor tissue samples will be used to evaluate changes in biomarker expression and genetic/genomic alterations. The analyses will help identify biomarkers that are predictive of response to the study drugs, and may help improve understanding of tumor development, tumor microenvironment and effects on peripheral immune activity for the study indications. Analyses may include, but may not be limited to, sequencing of DNA and/or RNA from tissue and/or blood (plasma) to look for genetic/genomic alterations (eg, mutations, copy number variation, mutational burden), IHC assessment of biomarker levels in tissue (eg, MET, PD-L1), and immune cell profiling by fluorescence-activated cell sorting (FACS) analyses. Immune cell profiling by FACS may be conducted at selected sites. These studies may use conventional as well as novel technology or methodology. The goal is to correlate modulation of these putative biomarkers to clinical outcome as a consequence of study treatment.

In addition, pharmacogenetic analyses involving single nucleotide polymorphism (SNP) genotyping may be performed in order to correlate variations in subject genotype with the safety/

tolerability, PK, and/ or pharmacodynamics (biomarker analyses) of cabozantinib and/or nivolumab/ipilimumab.

The biomarker assessment samples may also be used for diagnostic assay development related to study treatment and for the discovery of biomarkers that may prove to be valuable surrogates for clinical response as well as to understand the underlying mechanisms of the disease.

5.7.12 Overall Survival

Overall survival (OS) will continue to be assessed every 12 weeks (± 14 days) after the second post-treatment follow-up visit (FU-2), which occurs 100 (±14) days after discontinuation of study treatment. Subjects will be followed until death or Sponsor decision to no longer collect these data. Receipt of systemic NPACT will also be collected during follow-up contacts. If a subject withdraws consent for non-interventional study assessments, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations. These assessments are not required for subjects who discontinue study treatment in the Maintenance Phase (such subjects are to be followed per standard of care).

5.8 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the requirements or procedures of this protocol or from ICH GCP. Efforts should be made to limit deviations. The Investigator is responsible for promptly reporting protocol deviations as applicable to their IRB/EC and/or to the Sponsor per IRB/EC policy. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety, and determine whether additional reports or actions are required. For important or repeated protocol deviations, additional action may include site re-training, hold or closure of enrollment, and/or site termination.

6 TREATMENTS

6.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations. Special accommodations during the global COVID-19 pandemic are described in Appendix K.

6.1.1 Study Treatment: Cabozantinib in Combination with Nivolumab and Ipilimumab or Nivolumab and Ipilimumab

6.1.1.1 Cabozantinib (XL184) Tablets

The Sponsor will provide adequate supplies of cabozantinib, which will be supplied as 20-mg yellow film-coated round tablets. The components of the tablets are listed in Table 6-1.

Table 6-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	CCI
Cabozantinib Drug Substance (CCI drug load as free base)	Active Ingredient	
Microcrystalline Cellulose (Avicel® PH-102)	Filler	
Lactose Anhydrous (60M)	Filler	
Hydroxypropyl Cellulose (EXF)	Binder	
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	
Colloidal Silicon Dioxide	Glidant	
Magnesium Stearate	Lubricant	
CCI HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	

All study medication will be stored at controlled room temperature and inventoried according to applicable regulations. Further information on storage and handling will be provided in the pharmacy manual.

6.1.1.2 Cabozantinib-Matched Placebo Tablets

Subjects randomized to the control arm will receive cabozantinib-matched placebo indistinguishable in shape, size, color, and packaging from the active cabozantinib tablets. The composition of the placebo tablets is listed in Table 6-2. Dosing, storage and handling instructions are identical to that for the cabozantinib arm.

Table 6-2: Placebo Tablet Components and Composition

Ingredient	Function	CCI
Microcrystalline Cellulose (Avicel PH-102)	Filler	
Magnesium Stearate	Lubricant	
CCI HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	

6.1.1.3 Combination Treatment: Nivolumab and Ipilimumab

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Nivolumab injection for IV infusion is supplied as 100 mg/10 mL (10 mg/mL) single-dose vials. Each mL of nivolumab solution contains nivolumab (10 mg), mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. It may contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4 antigen. Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for IV infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. Ipilimumab injection for IV infusion is supplied as 200 mg/40 mL (5 mg/mL) single-dose vials. Each mL contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

Nivolumab and ipilimumab injections are to be administered as IV infusions through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. These agents are not to be administered as an IV push or bolus injection. Please refer to the nivolumab and ipilimumab local prescribing information or the 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.

Nivolumab 100 mg/10 mL (10 mg/mL) and ipilimumab 200 mg/40 mL (5 mg/mL) injections for IV use will be provided by the Sponsor.

6.2 Study Treatment Schedule of Administration

Two tablets of cabozantinib (20 mg each) or matched placebo once-daily (qd) will be administered orally.

Nivolumab will be administered at a dose of 3 mg/kg as an IV infusion once every 3 weeks (q3w) for the first four doses followed by the standard dosing regimen of 480 mg as an IV infusion once every 4 weeks (q4w) for no more than 2 years.

Ipilimumab will be administered at a dose of 1 mg/kg as an IV infusion q3w for a maximum of up to four doses. Subjects will receive the combination regimen with the first infusion of nivolumab and ipilimumab given on the same day as the first dose of cabozantinib or placebo.

The dose of nivolumab and ipilimumab will need to be adjusted based on the subject's current body weight on study should a change of at least 10% compared with baseline be documented.

Subjects will receive oral study treatment and (up to 2 years) nivolumab as long as they continue to experience clinical benefit as assessed by the Investigator or until unacceptable toxicity, the need for subsequent systemic anti-cancer treatment, or until any other reasons for treatment discontinuation listed in the protocol (Section 3.6).

For guidance on dose modifications, interruptions, delays, or discontinuations due to AEs, refer to Section 6.6.2 for cabozantinib and Section 6.6.3 for nivolumab/ipilimumab.

6.2.1 Study Treatment Administration on Week 1 Day 1 (W1D1)

Nivolumab and Ipilimumab:

Doses of nivolumab (3 mg/kg) will always be administered IV at the clinic by infusion on Day 1 of each 21-day cycles for the first 4 doses. Thereafter, doses (480 mg) will be administered on Day 1 of each 28-day cycle. In this study, treatment with nivolumab will be given for a maximum of 2 years from the start of study treatment.

Doses of ipilimumab (1 mg/kg) will always be administered IV at the clinic by infusion on Day 1 of each 21-day cycles for a maximum of four doses. Cycles may be longer if nivolumab or ipilimumab treatment is delayed due to toxicity or other reasons.

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 saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab study drug (approximately 30 minutes infusion) and will start after the infusion line has been flushed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes (from the end of the nivolumab infusion to the start of the ipilimumab infusion).

On W1D1, nivolumab and ipilimumab are to be administered before the oral study treatment.

The infusion of nivolumab and ipilimumab will be prepared according to the local prescribing information or the pharmacy manual. The IV administration of nivolumab and ipilimumab can only occur in a clinical setting with staff experienced in managing of infusion-related reactions and with access to emergency services.

Subjects should be carefully monitored for infusion reactions during IV administration. If an acute infusion reaction is noted, participants should be managed according to Section 6.6.3.

Cabozantinib/Placebo:

The subject will be fasted (with the exception of water) for at least 2 hours before receiving cabozantinib/placebo. Upon completion of the 2-hour fast, the subject will receive the oral dose of cabozantinib/placebo with a minimum of 8 oz (240 mL) of water in the clinic.

- After taking cabozantinib/placebo, the subject will continue to fast for a further 1 hour while under observation to monitor for potential AEs.
- If the subject develops an infusion reaction, the administration of oral study treatment will be delayed or interrupted until the subject has recovered and the Investigator believes that it is safe to administer cabozantinib/placebo.

For cabozantinib/placebo dosing on subsequent dosing days refer to Section 6.2.2.

6.2.2 Cabozantinib/Placebo Administration outside the Clinic

The subject should take cabozantinib/placebo outside the clinic at approximately the same time every day, preferentially before going to bed, and should adhere to the fasting requirements described in this section.

Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose. After the 2-hour fast and before going to bed, subjects are to take cabozantinib/placebo with a full glass of water (minimum of 8 oz or 240 mL) with no food intake for one hour post-dose. If the subject's schedule requires taking cabozantinib/placebo during the day, the subject is to be instructed to follow the same fasting recommendations.

Tablets should not be crushed or chewed. Grapefruit and Seville oranges (and products made from them) should be avoided while being treated with cabozantinib/placebo.

Subjects are to be instructed to not make up vomited doses and to maintain the planned dosing schedule. Subjects are not to make up for missed doses if more than 12 hours have elapsed after the time the subject would usually take cabozantinib/placebo. In the event of missed doses, subjects are not to take 2 doses to make up for the one the subject missed.

Any unused study treatment must be returned to the study site for drug accountability and disposal.

6.3 Treatment After Study Completion

After study completion (see Section 3.6.3), subjects who continue to demonstrate clinical benefit may be eligible to receive Exelixis-supplied study treatment for the maximum treatment duration specified in Section 6.2 during the Maintenance Phase. Alternatively, study treatment may be provided via a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of Exelixis.

Exelixis reserves the right to terminate access to Exelixis-supplied study treatment if any of the following occur:

a) the study is terminated due to safety concerns;

b) the development of nivolumab, ipilimumab, or cabozantinib is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives (eg, study is declared futile or the null hypothesis is not rejected for the primary endpoint of PFS);

c) the participant can obtain medication from a government-sponsored or private health program.

In all cases Exelixis will follow local regulations. Exelixis will work with study investigators to act in the best interest of subjects.

6.4 Compliance

Subject compliance with outpatient study treatment will be assessed by the site using drug dispensing and return records, infusion logs, progress notes about dose reductions/interruptions, and subject interview. These data will not be directly recorded in the CRF; rather, the CRF will capture infusion details and, for oral study treatment, intervals of constant dose and reasons for changes in dose level (eg, a new record completed each time dose level changes, including periods where no dose was taken, and the reason for a dose level change).

6.5 Study Treatment Accountability

The Investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Drug accountability will be performed periodically by the Sponsor or designee at interim monitoring visits. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

6.6 Safety Considerations

Subjects will be monitored for SAEs from the time of signing informed consent and for nonserious AEs from first dose of study treatment. Monitoring continues through 100 days for unrelated SAEs (Table 8-1) after the date of the decision to permanently discontinue all study treatment (defined as the later of the date of the decision to discontinue all study treatment or the date of the last dose of any study treatment). Longer monitoring periods are required for related SAEs and certain other events as described in Section 8.3. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix H. Subjects will be instructed to notify their physician immediately for any occurring AE. Causality assessment of AEs should include at minimum confounding factors such as disease and concomitant medications. Adverse event severity will be graded by the Investigator according to CTCAE v5.

The following should be taken into consideration in decisions regarding management for treatment-related side effects: cabozantinib, nivolumab, and ipilimumab have class-specific safety profiles based on their mechanisms of action but may also cause AEs that overlap.

- Examples of VEGFR-TKI associated AEs caused by cabozantinib are hypertension and hand-foot syndrome.

- Examples of irAEs caused by nivolumab are pneumonitis, colitis, hepatitis, nephritis, skin reactions, encephalitis, and endocrinopathies.

- Examples of irAEs caused by ipilimumab are hepatitis, endocrinopathies and hypophysitis.

- Examples of overlapping AEs are diarrhea and elevations in liver function tests (transaminases, bilirubin; see Section 6.6.1).

- As a general approach, all AEs should be managed with supportive care including both pharmacological and non-pharmacological treatments according to consensus management guidelines at the earliest signs of toxicity considered related to study treatment.

- Study treatment may be continued for mild AEs if appropriate supportive care has been initiated to ameliorate symptoms. Should this be ineffective and toxicities become unacceptable, dose modifications of study treatment should be considered to prevent worsening of toxicity. Moderate to severe AEs usually require dose modifications including dose reductions and/or interruptions.

- Dose interruptions of cabozantinib/placebo, nivolumab, or ipilimumab for AEs may occur at any time and independently at the discretion of the Investigator (for hepatocellular toxicity see below). If all study treatment is interrupted for more than 12 weeks, treatment should be discontinued unless approved by the Sponsor.

- In the case of AEs of *hepatocellular toxicity*, the Investigator should follow the guidance provided in Section 6.6.1, which summarizes the dose modification guidance for BOTH cabozantinib/placebo treatment as well as nivolumab/ipilimumab treatment.

- In the case of AEs of *non-hepatocellular toxicity*, the Investigator should follow the guidance on dose modifications of cabozantinib/placebo treatment in Section 6.6.2, and on dose modifications of nivolumab and ipilimumab in Section 6.6.3 with more detailed guidance in Appendix E.

6.6.1 Management of Hepatocellular Toxicity Associated with Cabozantinib/Placebo and Nivolumab/Ipilimumab

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib, nivolumab, and ipilimumab. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other causes (eg, cancer-related, infection) should be evaluated.

The following condition requires discontinuation of all study drugs:

- Drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with drug-induced liver injury (DILI).

Table 6-3 provides suggested guidance on management of hepatotoxicity related to cabozantinib/placebo and nivolumab/ipilimumab.

In the event cabozantinib/placebo is interrupted and nivolumab/ipilimumab delayed due to an increase of serum ALTor AST> 3.0 x ULN **or** serum total bilirubin > ULN to 1.5 x ULN, nivolumab and (if fewer than 4 ipilimumab doses have been administered and no AE has occurred that led to discontinuation of ipilimumab alone) ipilimumab should be resumed upon return of liver function tests to baseline grade, at which time cabozantinib/placebo should be resumed with a dose reduction (from either two tablets per day to one tablet per day, or one tablet per day to one tablet every other day, as appropriate).

If no additional ipilimumab is to be administered, the dose of cabozantinib/placebo should be re-escalated from one tablet per day to two tablets per day no sooner than 10 days after resumption of blinded oral therapy. Alternatively, if the subject had been taking one tablet every other day, then the dose of cabozantinib/placebo may be re-escalated to one tablet every day and, if tolerated, then to two tablets per day no sooner than 14 days thereafter.

Consult with the medical monitor to discuss further management should rechallenge be followed by any recurrence of increased liver function tests.

Dose delays should not alter the timing of other study assessments, including but not limited to tumor imaging scheduled based on W1D1 (≤ 3 days after randomization).

For additional information on dose modifications of nivolumab/ipilimumab treatment, refer to Section 6.6.3 and Appendix E.

Table 6-3: Suggested Management of Hepatotoxicity Associated with Study Treatment

Severity of LFT[a] Elevations by Laboratory Value	Dose Modification Guidance[b]	Management/Follow-up Guidance
AST or ALT > ULN to 3.0 x ULN **and/or** total bili > ULN to 1.5 x ULN, regardless of baseline value	• *Cabozantinib:* – Continue cabozantinib per protocol • *Nivolumab /Ipilimumab:* – Continue therapy per protocol	• Monitor LFTs per protocol. • Discontinue concomitant hepatotoxic medications, if possible.
AST or ALT > 3.0 x ULN to ≤ 5 x ULN **or** total bili > 1.5 x ULN to ≤ 3 x ULN, regardless of baseline value	• *Cabozantinib*: – Interrupt cabozantinib dosing. – If LFTs return to baseline grade, resume cabozantinib at a reduced dose. After completion of ipilimumab regimen, re-escalate cabozantinib dose as per protocol. If no additional ipilimumab doses are to be administered, the dose of cabozantinib may be re-escalated no sooner than 10 days after re-initiation of cabozantinib. – See Section 6.6.1 for additional guidance. • *Nivolumab /Ipilimumab:* – Delay therapy per protocol. – If LFTs return to baseline grade, resume therapy per protocol.	• Monitor LFTs twice weekly or more frequently as deemed clinically necessary. – If tapering off steroid therapy, monitor LFTs once weekly or more often per clinical judgment[c]. – If LFTs return to baseline grade, resume with routine monitoring. • If LFT elevations persist > 3 days or worsen: – Administer 0.5-1 mg/kg/day methylprednisolone or oral equivalent. – When LFTs return to baseline grade or CTCAE Grade ≤1, taper steroids over at least 1 month[c]. – Consider prophylactic antibiotics for opportunistic infections.
AST or ALT > 5 x ULN **or** total bili > 3 x ULN, regardless of baseline value	• *Cabozantinib*: – Discontinue cabozantinib if ALT or AST > 8 x ULN. – Otherwise interrupt cabozantinib dosing and resume at a reduced dose after LFTs return to baseline grade (Sponsor approval required) • *Nivolumab /Ipilimumab:* – Delay dose or permanently discontinue.	• Monitor LFTs twice weekly or more frequently as deemed clinically necessary. • During steroid taper, monitor LFTs once weekly or more often per clinical judgment[c]. • For AST or ALT > 5 x ULN to ≤ 20 x ULN, or total bilirubin > 3 x ULN to ≤ 10 x ULN: – Administer 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. • For AST or ALT > 20 x ULN, or total bilirubin > 10 x ULN: – Administer 2.0 mg/kg/day methylprednisolone IV or IV equivalent.

Severity of LFT[a] Elevations by Laboratory Value	Dose Modification Guidance[b]	Management/Follow-up Guidance
	* In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy must be obtained.	• Add prophylactic antibiotics for opportunistic infections. • Consult Gastroenterologist. • If LFT elevations do not improve in > 3 days, worsen or rebound: – Add mycophenolate mofetil 1g BID. – If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines. • Dosing may resume when laboratory values return to baseline. • Taper steroids over at least 1 month[c].
ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN **AND** no radiographic evidence of biliary obstruction	• All study drugs must be discontinued.	• Follow the above management/follow-up guidance by grade.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bili, bilirubin; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; LFT, liver function tests; ULN, upper limit of normal

[a] LFTs include AST, ALT and total bilirubin.

[b] For brevity, the term "cabozantinib" refers to blinded oral study treatment of cabozantinib or cabozantinib-matched placebo.

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

6.6.2 Management of AEs Associated with Cabozantinib/Placebo

Throughout the remainder of Section 6 the term "cabozantinib" refers to blinded oral study treatment of cabozantinib or cabozantinib-matched placebo. Considerations for management of AEs associated with oral study medication are presented below.

- The assigned dose for cabozantinib is 40 mg qd.
- Two dose reduction levels of cabozantinib (20 mg qd and 20 mg every other day [qod]) are permitted (see Table 6-4).

- Dose modification criteria for treatment-related AEs of cabozantinib are shown in Table 6-5. Grade 1 and tolerable Grade 2 AEs are managed similarly; Grade 3 and intolerable Grade 2 AEs are managed similarly.

- Dose reinstitution and reescalation after dose interruptions and/or reductions:

  - If the subject recovers from his or her toxicities to CTCAE v5 ≤ Grade 1 or to the baseline value (or lower) and the AE was unrelated to oral study medication, then oral study medication may be restarted with no change in dose.

  - If the subject recovers from his or her toxicities to ≤ Grade 1 or to the baseline value (or lower) and the AE was deemed related to oral study medication, then cabozantinib may be reinitiated but this must be at a reduced dose (see Table 6-4).

  - Subjects receiving a dose of 20 mg every other day (qod) may be restarted at the same dose if deemed safe at the discretion of the Investigator. Subjects unable to tolerate a dose of 20 mg qod must discontinue cabozantinib/placebo upon discussion with the Sponsor.

  - Re-escalation to the previous dose may be allowed at the discretion of the Investigator but no sooner than 10 days beyond improvement of AEs that led to the dose reduction to Grade 1 (or baseline value), as long as AEs are deemed tolerable and easily managed by optimized supportive treatment. Dose reescalation is not allowed following a cabozantinib-related dose reduction for Grade 4 hematologic toxicities or Grade 4 AEs affecting major organs (eg, central nervous system [CNS], cardiac, hepatic, renal, pulmonary GI).

- Guidelines for the management of specific AEs of cabozantinib such as GI disorders, non-GI fistula formation, hemorrhage, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, and respiratory disorders are provided in Section 6.6.2.1.

Table 6-4: Dose Reductions of Cabozantinib (Oral Dosing)

First Dose Level Reduction	Second Dose Level Reduction
20 mg daily (qd)	20 mg every other day (qod)

Cabozantinib must be discontinued upon discussion with the Sponsor if a dose of 20-mg cabozantinib every other day (minimum dose) is not tolerated.

Table 6-5: Dose Modifications for Cabozantinib-Related AEs

CTCAE v5 Grade	Recommended Guidelines for Management
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib at the current dose level if AE is manageable and tolerable.
Grade 2 AEs that are tolerable and are easily managed	Continue cabozantinib at the current dose level with supportive care.
Grade 2 AEs that are **intolerable** and **cannot be adequately managed**	Cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction of cabozantinib and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib must be interrupted immediately. In general, cabozantinib should be discontinued unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction of cabozantinib following recovery to Grade 1 (or baseline value) and optimal medical care Sponsor must be contacted to discuss treatment continuation upon resolution of AEs.

AE, adverse event.

Note: Cabozantinib dose modification criteria for specific medical conditions are provided in Section 6.6.2.1.

6.6.2.1 Warnings, Precautions, and Management Guidelines for Adverse Events Associated with Cabozantinib Treatment

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, PPE, constipation, hypertension, dysgeusia, dysphonia, and asthenia. For a full description of the safety profile of cabozantinib, refer to the cabozantinib Investigator Brochure.

Other medically important but less frequent AEs include arterial thrombotic AEs (eg, TIA, and MI) and venous thrombotic AEs (eg, DVT and PE), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; preferred term: posterior reversible encephalopathy syndrome).

Adverse events associated with laboratory test abnormalities that were experienced by ≥ 5% of cabozantinib-treated subjects in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, alkaline phosphatase (ALP) increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPE, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 6-4).

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

6.6.2.1.1 Gastrointestinal Disorders

Gastrointestinal (GI) perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2012) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects 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 6-6. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the 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 personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Following improvement in diarrhea, dose re-escalation should follow the guidelines listed in Section 6.6.2.

Table 6-6: Management of Diarrhea Associated with Cabozantinib

Status	Management

Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction
	• Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day])
	• Dietary modifications (eg, 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 > 48 h, or ≥ Grade 3	• Interrupt study treatment
	• Ask subject to attend clinic
	• Rule out infection (eg, stool sample for culture)
	  ○ Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h)
	• Administer fluids (1-1.5 L/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 h
	  ○ 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 (eg, 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

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 7.3 for further details).

6.6.2.1.2 Non-Gastrointestinal Fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

6.6.2.1.3 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

6.6.2.1.4 Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anti-cancer therapy. Deep vein thrombosis (DVT) and pulmonary embolism (PE) have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a PE and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with PE 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 and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

Arterial thrombotic events (eg, TIA, myocardial infarction) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

6.6.2.1.5 Hypertension

Table 6-7 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP

readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 6-7: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic and <100 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic and < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or sustained diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency[b]	• Discontinue cabozantinib treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 mm Hg or diastolic BP > 100 mm Hg based on their clinical judgment and assessment of the individual subject.

[b] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

6.6.2.1.6 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

6.6.2.1.7 Skin and Subcutaneous Tissue Disorders

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence, which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery (for tumor biopsies at least 10 days before the procedure). The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysesthesia (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms

such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPE are summarized in Table 6-8.

Table 6-8: Management of Hand-Foot Syndrome (PPE) Associated with Cabozantinib

CTCAE v5 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPE is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level[a]. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPE is tolerated. Cabozantinib should be dose reduced or interrupted if PPE is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume cabozantinib at a reduced dose if PPE recovers to Grade ≤ 1. Discontinue subject from study treatment if PPE does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPE, palmar plantar erythrodysesthesia.

[a] Permitted dose levels are defined by individual protocols.

6.6.2.1.8 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Advise subjects regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

6.6.2.1.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 6-9 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 6-9: Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 226.2 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption unless otherwise approved by the Sponsor. • If UPCR > 2 mg/mg, repeat UPCR monitoring within 7 days and once per week. If UPCR < 2 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.)
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR monitoring within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR monitoring, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of UPCR until it remains < 2 mg/mg on two consecutive measurements. If UPCR monitoring is determined to be stable (< 20% change) for 1 month then continue with UPCR monitoring per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment

UPCR, urine protein/creatinine ratio.

6.6.2.1.10 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

6.6.2.1.11 Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factors include decreased immune status (eg, after myelosuppressive anti-cancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.

6.6.2.1.12 Blood and Lymphatic System Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

6.6.2.1.13 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease-specific morbidities have been excluded when not prohibited.

6.6.2.1.14 Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

6.6.2.1.15 Corrected QT Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline per the site's ECG read, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or the average increase is > 60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment
- Immediately notify the Sponsor
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension), or those with a significant ventricular arrhythmia on ECG for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Send ECGs to central ECG laboratory for independent read
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms and the average increase is ≤ 60 ms above baseline, or a consulting cardiologist or appropriate expert determines that the frequency of ECGs may revert to the schedule in the protocol.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted but only at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed by a **cardiologist consultation.**
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms and ≤ 60 ms above baseline
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

Cabozantinib treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

6.6.2.1.16 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Table 6-5 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or IV replacement.

6.6.2.1.17 Endocrine Disorders

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

6.6.3 Management of AEs Associated with Nivolumab and Ipilimumab

The assigned dose for nivolumab is 3 mg/kg IV q3w for the first four doses followed by 480 mg IV q4w.

The assigned dose for ipilimumab is 1 mg/kg IV q3w for a maximum of up to four doses.

Dose reductions are not allowed for nivolumab or ipilimumab. AEs associated with nivolumab and ipilimumab are managed with dose delays.

For more detailed guidance on management of non-hepatocellular AEs associated with nivolumab and ipilimumab please see Appendix E. For recommendations on management of hepatocellular toxicity and dose modifications of both cabozantinib/placebo treatment and nivolumab/ipilimumab treatment, see Section 6.6.1

6.6.3.1 Immune-related Adverse Events (irAEs)

The immune-modulating properties of ICIs, such as the anti-PD-1 antibody nivolumab, and anti-CTLA-4 antibody ipilimumab are able to undermine immunologic tolerance and generate a subset of AEs (called immune related AEs or irAEs) with an autoimmmune inflammatory pathomechanism. IrAEs may involve every organ or tissue (Michot et al 2016). Most irAEs occur within the first 12 weeks of exposure to ICIs but some of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs such as nivolumab are fatigue, fever, and chills. Organ-specific irAEs consist of pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, skin adverse reactions, encephalitis, myocarditis, and endocrinopathies (hypophysitis, adrenal insufficiency, hyperglycemia).

Early recognition and management of irAEs associated with immuno-oncology agents may mitigate severe toxicity. Medical management of irAEs focuses on suppressing the immune response with non-steroidal and steroidal anti-inflammatory medication. Management algorithms have been developed and should be followed for subjects with suspected irAEs. Further information on management of nivolumab/ipilimumab-associated irAEs is provided in Section 6.6.3.2 and Appendix E, and can also be found in the US PI.

6.6.3.2 Dose Modification Criteria for Nivolumab and Ipilimumab

For dose modification criteria and management of AEs related to hepatotoxicity, refer to Table 6-3. For other AEs categorized by SOC, refer to Table 6-10. Further criteria and guidance for dose delays, resumptions and discontinuations of nivolumab and ipilimumab are provided in Sections 6.6.3.2.1 and 6.6.3.2.2.

Table 6-10: Adverse Event Criteria for Dose Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-Related AEs per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose.	Dosing may resume when AE resolves to baseline.
	Grade 3	Nivolumab monotherapy: Delay dose.	Dosing may resume when AE resolves to baseline.
		When administered with ipilimumab: Permanently discontinue Ipilimumab.	Nivolumab monotherapy may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab monotherapy, permanently discontinue.
	Grade 4	Permanently discontinue.	-
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose.	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue.	-
Pulmonary			
Pneumonitis	Grade 2	Delay dose.	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue.	-

Drug-Related AEs per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Endocrinopathy • May resume treatment if drug-related endocrinopathies adequately controlled with only physiologic hormone replacement.			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose.	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue.	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose.	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue.	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis or Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose.	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue.	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.

Drug-Related AEs per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperthyroidism or -Hypothyroidism	Grade 2 or 3	Delay dose.	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue.	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose.	Dosing may resume when rash reduces to ≤ 10% body surface area.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose.	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area.
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue.	-
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue.	-
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue.	-
Encephalitis	Any Grade encephalitis	Delay dose.	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue.	-

Drug-Related AEs per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Myelitis	Any Grade myelitis	Delay dose.	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue.	-
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose.	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue.	-
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose.	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue.	-
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose.	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.
	Grade 4	Permanently discontinue unless an alternative etiology (such as pancreatic metastases) fully explains the findings.	-
Uveitis	Grade 2 uveitis	Delay dose.	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue.	-

Drug-Related AEs per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Drug-Related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose.	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose.	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting > 7 days	Permanently discontinue.	-
	Recurrence of Grade 3 AE of any duration	Permanently discontinue.	-
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue.	-
Other Lab abnormalities			
Other drug-related lab abnormality **(not listed above)**	Grade 3	Delay dose.	Exceptions: No delay required for Grade 3 lymphopenia. Permanent Discontinuation for Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue.	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue.	Refer to Section 6.6.3.3 on treatment of nivolumab/ipilimumab-related infusion reactions.

DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; SJS, Suspected Stevens-Johnson syndrome; TEN, Toxic Epidermal Necrolysis

6.6.3.2.1 Dose Delay and Restart Criteria for Nivolumab and Ipilimumab

Immuno-oncology agents, such as nivolumab and ipilimumab, are associated with AEs that differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

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

In addition to criteria and guidelines in Table 6-10, subjects may resume treatment with these study drugs when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Systemic corticosteroids for control of infusion reactions or irAEs must have been tapered to a dose level ≤ 10 mg/day of prednisone equivalent before resuming treatment with nivolumab/ipilimumab.
- If all study treatment is interrupted for > 12 weeks, the subject must be permanently discontinued from study treatment unless approved by the Sponsor.

Refer to Appendix E for a complete list of criteria for resumption of nivolumab and ipilimumab treatment.

6.6.3.2.2 Criteria for Discontinuation of Nivolumab and Ipilimumab

If a subject meets criteria for discontinuation and the investigator is unable to determine whether the event is related to one or both checkpoint inhibitors, the subject should discontinue both nivolumab and ipilimumab with the exception of certain cases of liver function test elevation (See Section 6.6.1).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue as clinically indicated during such dosing delays.

6.6.3.3 Treatment of Nivolumab and Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.

Regardless of whether the event is attributed to these study drugs, all Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Sponsor Medical Monitor or designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to CTCAE v5 guidelines.

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

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

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

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 these study drugs. 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. Nivolumab + ipilimumab 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 CONCOMITANT MEDICATIONS AND THERAPIES

7.1 Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

- Adrenal replacement steroid doses at > 10 mg daily prednisone equivalent are permitted.

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).

- Bisphosphonates or RANK-L inhibitors can be used per standard of care if the benefit outweighs the risk per the Investigator’s discretion

  Note: osteonecrosis of the jaw (ONJ) has been reported in subjects using bisphosphonates. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.

- Inhaled, intranasal, intra-articular, and topical corticosteroids are allowed if minimal systemic absorption. Systemic corticosteroids are allowed for control of infusion reactions or irAEs and must be tapered to a dose level ≤ 10 mg/day of prednisone equivalent before next nivolumab/ipilimumab administration. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed.

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

    - *Low dose low molecular weight heparins (LMWH) for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.

    - *Therapeutic doses of LMWH* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 1 week, and has had no complications from a thromboembolic event or the anticoagulation regimen.

    - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.6.2.1.4.

    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction).

    - For restrictions on oral anticoagulants see Section 7.2.

Potential drug interactions with cabozantinib are summarized in Section 7.3.1. The drug interaction potential of nivolumab is unknown as no formal PK drug-drug interaction studies have been conducted (nivolumab US prescribing information).

7.2 Prohibited or Restricted Therapy

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines), unless blinded oral study treatment has been permanently discontinued.
- Any non-protocol systemic anti-cancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs specifically for the treatment of the cancer under investigation).
- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 7.1 except when both nivolumab and ipilimumab have been permanently discontinued.
- Live vaccines are prohibited during treatment and until 100 days after the last doses of nivolumab and ipilimumab (eg, intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).
- The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anti-cancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established. If clinically unavoidable, the Investigator should consult the Sponsor prior to the procedure for safety guidance.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment

(refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided (Appendix G). Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided (Appendix G). Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 7.3.1.

The US prescribing information for nivolumab and ipilimumab notes that no formal PK drug-drug interaction studies have been conducted using these agents.

7.3 Potential Drug Interactions

7.3.1 Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration-vs-time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided (Appendix G). Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib (Appendix G). Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the drug interaction tables at the following website for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib, because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, so fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein (eg, fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). In addition, cabozantinib was shown to be a substrate of drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay. Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (eg, cyclosporine, efavirenz, emtricitabine) should be approached with caution.

Additional details related to these overall conclusions can be found in the cabozantinib Investigator Brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the cabozantinib Investigator Brochure.

7.3.2 Potential Drug Interactions with Nivolumab and Ipilimumab

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of nivolumab. No formal drug interaction studies for nivolumab and ipilimumab have been conducted (nivolumab and ipilimumab US prescribing information).

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. This requirement

includes specific events or symptoms associated with cancer progression or general clinical deterioration to ensure potential toxicities are not overlooked. Radiographic progression without associated clinical sequelae is not considered an AE: terms such as 'disease progression' should be avoided. Pre-existing medical conditions that worsen during a study will be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 8.1.2.

All untoward events that occur through 30 days (100 days for SAEs and certain other events [Table 8-1]) after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to discontinue all study treatment or the date of the last dose of any study treatment) are to be recorded by the investigational site. Further details are provided in Appendix H.

At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report.

Assessment of the relationship of the AEs to individual study drug by the Investigator will be based on the following two definitions:

- **Not Related**: An event is assessed as not related to study drug if it is attributable to another cause and/or there is no evidence to support a causal relationship.
- **Related**: An event is assessed as related to study drug when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study treatment and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

8.1.2 Laboratory Abnormalities

All laboratory data required by this protocol and any other clinical investigations will be reviewed by the Investigator. Any abnormal value that leads to a change in subject management (eg, dose reduction, delay, or study drug discontinuation, or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the Investigator will be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

8.2 Serious Adverse Events

8.2.1 Definitions

The SAE definition and reporting requirements are in accordance with the International Conference on Harmonization (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose

- Results in death.
- Is immediately life-threatening (ie, in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
- Results in significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

As soon as an investigator becomes aware of an AE that meets the criteria for an SAE, the Investigator will document the SAE to the extent that information is available.

SAEs, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites.

SAEs that must be recorded on an SAE Reporting form include the following:

- All SAEs that occur after informed consent and through 100 days after the date of the decision to permanently discontinue study treatment ie, the later of the date of the decision of

the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by the subject (or the date the subject is deemed to be a screen failure).

- Any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 100 days after the date of the decision to permanently discontinue study treatment.

Note: If the subject does not meet the eligibility criteria during screening, then SAEs only need to be reported from the time the subject signs the informed consent until the day when the subject has been determined to not be eligible for study participation.

SAEs that occur after the initial consent and through 100 days after the date of the decision to permanently discontinue study treatment must also be recorded on the CRF page.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, and an event description. Other important information requiring timely reporting are the SAE term(s), the reason why the event is considered to be serious (ie, the seriousness criteria), and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by the Sponsor's Drug Safety personnel or designee.

When reporting SAEs, the following additional points will be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator will report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.

- Death will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when the etiology has been identified. If an autopsy was performed, the autopsy report should be provided.

- While most hospitalizations necessitate reporting of an SAE, hospitalizations that do not require SAE reporting are as follows:
    - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
    - Prespecified study hospitalizations for observation.
    - Events that result in hospital stays of less than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).
- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

8.2.2 Regulatory Reporting

Exelixis Drug Safety group (or designee) will process and evaluate all SAEs as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

Exelixis Drug Safety group (or designee) will assess the expectedness of each SAE to the study treatment using the current reference safety information (RSI) for each study drug.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with FDA regulations (21 Code of Federal Regulations [CFR] 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the Investigator to his or her IRB/ECs will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

As a general rule, the treatment blind will be broken by authorized Sponsor and/or CRO personnel prior to reporting an SAE that meets the criteria for expediting reporting to the Regulatory Authorities and to some central ECs. Other than those involved in the unblinding and

submission processes, the Investigator, Sponsor, and CRO staff will remain blinded to the treatment assignment.

8.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) consist of immune-mediated AEs associated with ICIs, cases of potential DILI, and suspected transmission of an infectious agent by the study treatment (Table 8-1).

AESIs will be reported to the Sponsor or designee using the SAE reporting form irrespective of whether the event is serious or nonserious; all AESIs must be reported within 24 hours using the SAE process as described in Section 8.2.

Guidance for management of immune-mediated AEs is provided in the protocol (Section 6.6.3) and can also be found in the local prescribing information for nivolumab and ipilimumab.

Table 8-1: Adverse Events of Special Interest

Event
• Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: o Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN o Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
• Suspected transmission of an infectious agent by the study treatment, as defined below o Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
• Pneumonitis
• Colitis
• Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
• Hepatitis, including AST or ALT > 10 × ULN
• Systemic lupus erythematosus
• Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
• Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
• Nephritis
• Ocular toxicities (eg, uveitis, retinitis)
• Myositis
• Myopathies, including rhabdomyolysis
• ≥ Grade 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
• Vasculitis

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal. All events that meet the listed criteria should be reported regardless of Investigator attribution to study treatment.

8.3.1 General Information on Immune-Related Adverse Events

The immune-modulating properties of immune checkpoint-inhibitors are able to undermine immunologic tolerance and generate a subset of AEs (called irAEs) with an autoimmmune inflammatory pathomechanism. Immune-related AEs may involve any organ or tissue (Michot et al 2016). Most irAEs occur within the first 12 weeks of exposure to ICIs but some may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs are fatigue, fever, and chills. Organ-specific irAEs consist of dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and

endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively unspecific symptoms. The following additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), FT4 and TSH (pituitary-thyroid function), luteinizing hormone (LH) and follicle-stimulating hormone (FSH; pituitary-gonadal function), adrenocorticotropic hormone (ACTH) and cortisol (pituitary-adrenal function).

Additional organ-specific irAEs include hepatitis (AST/ALT increases, hepatomegaly, periportal edema, periportal lymphadenopathy, lymphocyte infiltration of periportal tissue and surrounding primary biliary ducts) and pneumonitis (acute interstitial pneumonia). Less frequent irAEs include neurologic syndromes (myasthenia gravis, Guillian-Barré syndrome, aseptic meningitis), ocular AEs (uveitis), renal AEs (interstitial nephritis), cardiac AEs (myocarditis), and pancreatic AEs (lipase increase).

8.4 Follow-Up of Adverse Events

Nonserious AEs (see below for AESIs [Table 8-1]) are to be recorded in the CRF until 30 days after the date of the decision to discontinue study treatment (the later of the date of the decision by the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by the subject). The status of unrelated SAEs that are ongoing after the date of the decision to discontinue study treatment will be documented until the 100-day FU-2 visit.

All AESIs (regardless of seriousness) and all related SAEs that are ongoing 100 days after the date of the decision to discontinue study treatment (the later of the date of the decision by the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by the subject), and AEs assessed as related that led to study treatment discontinuation that are ongoing 100 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to Grade 2 or lower
- The investigator determines that the event has become stable or irreversible.

Further details on follow-up procedures are provided in Appendix H.

8.5 Other Safety Considerations

8.5.1 Pregnancy

Use of highly effective methods of contraception (Appendix D) is very important during the study and must continue for 5 months for women, and 7 months for men, after the last dose of study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have follow up for at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, the Sponsor will ask the pregnant female partner to consent to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth. Both male and female subjects should seek advice and consider fertility preservation before receiving study treatment.

The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to the Sponsor or designee. Any birth defect or congenital anomaly must be reported as an SAE and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Females should not breastfeed while receiving study treatment and for up to 5 months from the last dose of nivolumab or up to 4 months from the last dose of cabozantinib.

8.5.2 Medication Errors/Overdose

Medication error is defined as the administration of each study drug medication outside or above the established dosing regimens per the specific protocol.

Any study medication overdose, misuse, abuse, or study medication error (excluding missed doses) that results in an AE or SAE requires reporting to the Sponsor or designee according to the guidance for AE and SAE reporting (Sections 8.1 and 8.2, respectively).

In case of overdose, the Sponsor Medical Monitor or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice. Please refer to the cabozantinib Investigator Brochure for additional management recommendations regarding overdoses of cabozantinib and to Appendix E regarding overdoses of nivolumab or ipilimumab.

9 STATISTICAL CONSIDERATIONS

Details of the planned analyses, including any modifications implemented prior to conducting analyses, will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before the primary endpoint analysis is performed. Any sensitivity analyses or other strategies if needed to assess and address consequences of the COVID-19 pandemic on trial conduct and study data will be provided in the SAP. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

9.1 Analysis Populations

The following populations will be employed for statistical analyses.

9.1.1 Intention-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all subjects who are randomized, regardless of whether any study treatment or the correct study treatment is received.

9.1.2 PFS Intention-to-Treat Population

The first 440 subjects that are randomized (based upon Greenwich Mean Time randomization date/time values) will be considered as the PFS Intent-to Treat (PITT) population.

9.1.3 Safety Population

The Safety population will consist of all subjects who receive any amount of study treatment. Subjects who receive any amount of cabozantinib in error will be summarized in the experimental (cabozantinib plus nivolumab and ipilimumab) arm.

9.2 Study Endpoints

9.2.1 Definitions

9.2.1.1 Duration of Progression Free Survival

Duration of PFS is defined as the time from randomization to the earlier of the following events: PD as determined by the BIRC per RECIST 1.1 or death due to any cause. The definition of radiographic PD and censoring rules for the primary analysis are described in Section 9.2.2.1.

9.2.1.2 Duration of Overall Survival

Duration of OS is defined as the time from date of randomization to date of death due to any cause. For subjects who are alive at the time of data cutoff or are permanently lost to follow-up, duration of OS will be right censored at the date the subject was last known to be alive.

9.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of PFS per RECIST 1.1 as determined by BIRC.

9.2.2.1 Primary Analysis: Progression-Free Survival

The primary analysis of PFS is event-driven and will be conducted after at least 249 events have been observed in the PITT population (see Section 9.1.2). It is designed to include only progression events as determined by the BIRC per RECIST 1.1. Clinical deterioration or radiographic progression determined by the Investigator will not be considered progression events.

General censoring rules for the primary analysis of PFS are described below:

- Subjects who receive systemic NPACT or surgical resection of target tumor lesion(s) before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of subsequent therapy or surgery.
- Subjects who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment.
- Subjects who miss 2 or more scheduled tumor assessments followed by an event will be right censored on the date of their most-recent tumor assessment prior to the missing assessments.

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided 0.05 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

In the primary analysis of PFS, if the p-value for the stratified log-rank test is statistically significant and the HR ($\lambda_{\text{cabozantinib + nivolumab/ipilimumab}}$/ $\lambda_{\text{nivolumab/ipilimumab+placebo}}$) is < 1, the null hypothesis of no difference between the two treatment arms in PFS will be rejected and it will be inferred that PFS is superior in the group receiving cabozantinib plus nivolumab/ipilimumab compared with the group receiving nivolumab/ipilimumab plus placebo.

Analyses of PFS based upon investigator assessment will follow the same methods.

9.2.2.2 Supportive Analyses

Supportive (sensitivity) analyses will be conducted using all PFS events and subjects in the ITT population at the time of the primary PFS analysis in the PITT population. Additional sensitivity analyses of PFS will be defined in the SAP using alternative event definitions and censoring schemes to account for partial or completely missing assessments, address bias due to tumor assessment timing, and to evaluate the impact of potentially informative censoring. These analyses will be performed using the same statistical methods described for the primary analysis.

Exploratory analyses of the effect of baseline characteristics, stratification factors, and other variables on PFS will be conducted using Cox regression models and subgroup analyses performed employing Kaplan-Meier methods.

9.2.3 Secondary Efficacy Endpoint

The secondary efficacy endpoint for this study is duration of OS. Formal hypothesis testing is planned for this endpoint.

9.2.3.1 Overall Survival

The primary analysis of OS is event-driven and will be conducted after at least 433 deaths have been observed in the ITT population (Section 9.1.1).

Hypothesis testing between the two treatment arms will be performed using the stratified log-rank test with a 2-sided 0.05 level of significance. The stratification factors are those used to stratify the randomization (see Section 3.4).

The median duration of OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR with 95% CIs will be estimated using a Cox regression model and will include the same stratification factors described above.

Three interim analyses of OS are planned. Details are provided in Section 9.6.

At any analysis of OS (interim or final), if the p-value for the stratified log-rank test is statistically significant and the HR ($\lambda_{\text{cabozantinib + nivolumab/ipilimumab}}$/ $\lambda_{\text{nivolumab/ipilimumab+placebo}}$) is < 1, the null hypothesis of no difference in OS between the two treatment arms will be rejected and it will be inferred that OS is superior in the group receiving cabozantinib plus nivolumab/ipilimumab compared with the group receiving nivolumab/ipilimumab plus placebo.

9.2.4 Additional Endpoints

Details of the planned analyses of these endpoints will be provided in the SAP:

- ORR per RECIST 1.1 by BIRC
- PFS and ORR per RECIST 1.1 by BIRC according to PD-L1 status
- PFS and ORR per RECIST 1.1 as assessed by the Investigator
- Duration of radiographic response as assessed by the Investigator and by BIRC
- Safety through the evaluation of AEs, including irAEs, and other safety assessments.
- PK of cabozantinib given in combination with nivolumab and ipilimumab
- Immunogenicity of nivolumab and ipilimumab given in combination with cabozantinib
- Correlation of biomarker analyses with clinical outcomes
- Health-related quality of life (HRQoL) as assessed by the EuroQol Health questionnaire instruments (EQ-5D-5L)
- Health care resource utilization

9.3 Control of Type I Error

Inflation of Type 1 error associated with testing multiple endpoints (primary and secondary) will be controlled by applying a hierarchical testing procedure: OS will be tested only if the null hypothesis of no difference between arms in PFS is rejected.

Three interim analyses of OS are planned (see Section 9.6). Inflation of Type 1 error associated with interim analyses will be controlled using a Lan-DeMets O'Brien-Fleming alpha-spending function.

All other statistical evaluations of efficacy will be considered exploratory.

9.4 Safety Analyses

All safety analyses will be performed using the Safety population. No formal statistical comparisons between the two treatment arms are planned.

9.4.1 Adverse Events

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The Investigator will classify the severity of AEs using the CTCAE v5 and will judge each event to be "not related" or "related" to study treatment.

A treatment emergent adverse event (TEAE) is defined as any event that begins or worsens on or after date of first dose of study treatment. Only TEAEs with an onset date prior to date of decision for treatment discontinuation (the later of the date of the decision of the Investigator to permanently discontinue study treatment or the date of the last dose of study treatment taken by

the subject) + 30 days (+ 100 days for SAEs and certain other AEs; Section 8.3) will be tabulated in summary tables.

The frequency and percentage of subjects with TEAEs will be tabulated for overall incidence by system organ class and/or preferred term by treatment arm. Related TEAEs, serious TEAEs, related serious TEAEs, high-grade TEAEs, Grade 5 TEAEs, and TEAEs resulting in study treatment discontinuation will be similarly summarized. Summaries by worst reported severity for each event within a subject will also be provided.

At each level of summarization, a subject will be counted only once for each AE preferred term he/she experiences within that level (ie, multiple episodes of events with the same preferred terms will be counted only once).

All reported subject deaths will be summarized by treatment group, cause of death, and relationship to study treatment.

9.4.2 Laboratory Test Results

Laboratory test results will be summarized by treatment group to evaluate worst post-baseline CTCAE grade and shifts or changes from baseline.

9.4.3 Other Safety Endpoints

Changes or shifts from baseline in vital signs, performance status, and QTc interval will be summarized by treatment group.

The number of subjects experiencing dose reduction (cabozantinib only), interruption, and/or discontinuation due to an AE will be provided.

Concomitant medications will be standardized using the World Health Organization drug dictionary and summarized by class and preferred term.

9.5 Power and Sample Size

The study is designed to provide adequate power for both PFS and OS. A larger sample size is needed to provide reasonable power for OS than for PFS. As a result, if PFS is evaluated in the entire study sample, the PFS events may be biased toward shorter progression times. Thus, to allow longer, more robust PFS follow up among a fewer number of subjects this study employs a "trial within a trial design." The primary analysis of PFS will be conducted after at least 249 PFS events have been observed among the first 440 randomized subjects, defined as the PFS Intent-to-Treat (PITT) population.

For PFS, a total of 249 events in the first 440 randomized subjects provides the study with 90% power for a 2-sided log-rank test with a 5% level of significance to detect a HR of 0.66. Assuming an exponential distribution of PFS, this corresponds with a 52% increase in median PFS from 11.6 months to 17.6 months. In the current design, the minimum observed effect that would result in statistical significance for PFS is a HR of 0.78, a 28% improvement in median from 11.6 to 14.9 months. Interim analysis of PFS is not planned.

For OS, the study was originally designed as follows: a total of 342 deaths among 676randomized subjects are required to provide 90% power to reject the null hypothesis of no difference in OS using the log-rank test, a 2-sided significance level of 5%, three planned interim analyses (see Section 9.6), and assuming a true HR of 0.70. Assuming an exponential distribution for OS, this corresponds to a 43% improvement in median survival from 41 months to 58.6 months. Under this design, the minimum observed effect that would result in statistical significance for the final analysis of OS is an HR of 0.80, a 25% improvement in median from 41 to 51.1 months; a minimum difference in observed medians of approximately 10 months.

In response to new data supporting a median OS in the control arm of 48 months instead of the previously assumed 41 months (Albiges et al 2020), the study has been modified as follows: A total of 433 events among 840 randomized subjects (the ITT population) are required to provide 90% power to reject the null hypothesis of no difference in OS using the log-rank test at a 2-sided significance level of 5%, 3 planned interim analyses (see Section 9.6), and assuming a true HR of 0.73. Assuming an exponential distribution for OS, this corresponds to a 37% increase in median survival from 48 months to 65.8 months. Under this design the minimum observed effect that would result in statistical significance for OS is an HR of 0.824, a 21% improvement in median from 48 to 58.25 months; a minimum observed difference in medians of approximately 10 months.

This increase in sample size does not inflate Type 1 error because (a) it was done solely in response to new external data about the expected median OS of the control arm, and (b) the control arm median is a nuisance parameter with respect to the minimum observed difference in medians that results in rejection of the null hypothesis. This change ensures the trial retains the ability to reject the null hypothesis for OS if the observed difference in medians is approximately 10 months.

With an assumed constant accrual rate of 40 subjects per month, a 1:1 treatment allocation ratio, and 3 interim analyses of OS, a total of 840 subjects (420 per treatment arm) is required to observe the required number of events within the planned study duration (approximately

21 months accrual; approximately 23 months after first subject randomized to observe the required PFS events among 440 subjects and approximately 69 months after first subject randomized to observe the required deaths for OS among 840 subjects). The true intervals required to meet these milestones may be longer or shorter due to divergence from assumptions, including non-constant accrual rate due to the time required for all study sites to become active.The PITT population may be expanded by 25% from the first 440 to the first 550 randomized if a review of accumulating PFS events suggests that the 249 events required for the analysis will not be reached due to censoring caused by a higher than expected study drop-out or non-compliance stemming from the COVID-19 pandemic.

An overview of the endpoints and operating characteristics is shown in Table 9-1:

Table 9-1 Summary of Endpoint Analysis

Accrual per month	40	
Randomization allocation	1:1	
Endpoint:	**PFS: Primary endpoint**	**OS: Secondary endpoint**
Power	90%	90%
Alpha allocated (2-sided)	0.05	0.05
# of interim analyses (approximate information fraction)	1 (40%) Futility, non-binding (1-sided)	3 (27%, 50%, 75%) Efficacy
Assumed median, control (months)	11.6	48
Assumed median, experimental (months)	17.6	65.8
Assumed HR	0.66	0.73
Number of events	249	433
N for analysis	440 (PITT population)	840 (ITT Population)
Time to enroll (months)	11	21
Time to trigger event (months)	23	69
Maximum HR to reject Ho (experimental median in months)	0.78 (14.9)	0.824 (58.25)
Minimum difference in medians (months) to reject Ho (under standard assumptions)	3.3	10.25

9.6 Interim Analyses

The number of events required to evaluate OS is based upon the most accurate assumptions currently available and provides high power to detect the smallest clinically meaningful difference in OS under these assumptions. However, as there is uncertainty in the assumptions, interim analyses provide an opportunity to stop the trial early if the treatment benefit of the experimental arm is larger than expected, potentially allowing the new regimen to become available sooner to this patient population.

Three interim analyses of OS are planned at approximately the 27%, 50% and 75% information fractions, employing a Lan-DeMets O'Brien-Fleming alpha-spending function. Details and boundaries for these interim and the final analysis are shown in the table below:

	1st Interim	2nd Interim	3rd Interim	Final
Approximate information fraction	27%	50%	75%	100%
Approximate # of events	117	217	325	433
Maximum HR to reject Ho	0.464	0.668	0.77	0.824
Critical p-value to reject Ho	0.0000324	0.003	0.018	0.044

Rejection of the null hypotheses for OS at the first interim analysis at about 27% information is not expected: it is designed primarily as an administrative analysis, will coincide with the primary analysis of PFS and will be performed only if the null hypothesis for PFS is rejected.

Due to logistical considerations in event ascertainment and operational planning and conduct, the actual analyses may include more or fewer events than the target information fractions. The actual critical values employed at the interim and final analyses of OS will depend upon the actual information fraction at the time of the analyses.

If null hypothesis of no differences in OS is rejected at a planned interim OS analysis in favor of the arm with cabozantinib plus nivolumab/ipilimumab, no subsequent testing of OS is planned.

To help limit exposure to the experimental regimen should interim data suggest it is unlikely to demonstrate superior efficacy, a non-binding futility analyses of PFS is planned to be performed at the 40% information fraction (approximately 100 events) for PFS. The analysis will be based upon radiographic evaluations per the BIRC. Results will be reviewed by the IDMC and actions taken as described in Section 12.2.

10 OTHER ANALYSES

10.1 Pharmacokinetic Analyses

The plasma concentration of cabozantinib will be analyzed by designated laboratory using a validated bioanalytical method. Descriptive statistics (eg, number, mean and/or median, standard deviation, and coefficient of variation) will be used to summarize the concentration-time data per visit. Where appropriate, these data may be combined with data from other studies as part of a meta-analysis (ie, population PK analysis) The effect of cabozantinib exposure on biomarkers, clinical safety parameters (eg, selected AEs) or clinical response may also be explored.

Serum concentrations of nivolumab and ipilimumab will also be measured and summarized by visit.

10.2 Immunogenicity Analyses

Results of anti-drug antibody (ADA) testing (immunogenicity) will be summarized overall as the number of subjects with ADA at any time point. The association between human ADA incidence, PK, and efficacy and/or safety outcomes may be explored.

10.3 Biomarker Analyses

Analyses may include MET and PD-L1 expression and other analyses (eg, TMB) with clinical response.

11 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the Investigator. Authorized study site personnel will enter data directly into a computerized eCRF database (ie, electronic data capture [EDC] system). Study databases will be subject to electronic and manual quality assurance procedures.

12 STUDY COMMITTEES

12.1 Executive Safety Committee (ESC)

The Sponsor's Executive Safety Committee (ESC) provides safety oversight over periodic and ongoing reviews on product safety data and blinded study data (through a Safety Management Team). The ESC provides the company position and actions for all safety aspects of the company's product to protect patient safety and public health. The Sponsor's ESC is managed and chaired by the Head of Drug Safety, and includes the following other members: Chief Medical Officer, Head of Clinical Development, Head of Regulatory Affairs, and qualified representatives of other functional groups as appropriate.

12.2 Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects and will not be authors on publications resulting from the study. IDMC members will be selected for their expertise in oncology.

This IDMC will convene regularly, including a safety assessment after a total of 30 subjects have been randomized and followed for at least 6 weeks. The primary responsibilities of the IDMC are to:

- Review the accumulating safety data on a regular and an ad hoc basis
- Make recommendations to the Sponsor regarding the continued conduct of the study based upon their evaluation of safety and efficacy data
- Review the results of a futility analysis of PFS (as described in Section 9.6) and make a recommendation, described below.

Safety data will be provided at regular intervals to the IDMC in the form of unblinded summary reports or data listings. To allow the evaluation of safety in the context of potential benefit, OS data (including Kaplan-Meier curves) may be reviewed by the IDMC at the time of safety summary reviews. The IDMC will have access to subjects' individual treatment assignments.

General stopping rules are as follows:

- The IDMC members will use their expertise, experience and judgment to evaluate the safety data from the trial and recommend to Exelixis whether the trial should continue, be modified, or be stopped early for safety concerns. No formal rules for making these recommendations based upon safety data are planned.

For the futility analysis (described in Section 9.6):

- If the results of the futility analysis yield an observed HR for PFS per BIRC of < 1.059 (and in the absence of significant safety concerns), the IDMC will recommend the trial continue. Note that the boundary of 1.059 is based on the 40% information fraction and may have to be recomputed based on the actual number of events observed.

- If the results of the futility analysis yield an observed HR for PFS per BIRC of ≥ 1.059, the IDMC will refer the analysis results and a recommendation to a Sponsor Executive Committee (composed of individuals not involved in day-to-day trial conduct). The Executive Committee will review the analysis results and IDMC recommendation to make a decision about whether the trial will continue or be declared futile.

- If the trial is declared futile, study actions may include, but are not limited to discontinuing enrollment and/or discontinuing study treatment for study subjects.

The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to the Sponsor's senior management.

Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate IDMC charter.

12.3 Blinded Independent Radiology Committee (BIRC)

A BIRC will be established to evaluate tumor scans and prior radiation history data of trial subjects in a central, blinded, and independent fashion (see also Section 5.7.6.3). The BIRC will be comprised of board-certified radiologists who will determine radiographic response and

progression following randomization. Additional imaging results may be requested by the Sponsor for BIRC review.

Additional details regarding BIRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the BIRC Charter.

12.4 Clinical Steering Committee (CSC)

The Clinical Steering Committee consists of physicians who have an expertise in treating patients with RCC. The CSC will provide critical scientific guidance including, but not limited to, protocol design and implementation and interpretation of clinical study results.

13 ETHICAL ASPECTS

13.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

13.2 Informed Consent

Sample ICFs will be supplied to each site. The Sponsor or its designee must review any proposed deviations from the sample ICF. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject If applicable, the ICF will be provided in a certified translation of the subject's language.

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in

significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, will be given a copy of the revised form, and must give their consent to continue in the study.

13.3 Institutional Review Board/ Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/ EC approval to the Sponsor (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

13.4 Disposition of Subject Samples

Protocol-defined analyses are anticipated to result in depletion of all or almost all research samples. If a subject requests destruction of their tissue and blood samples, the Sponsor will make every attempt to destroy the samples. The Sponsor will notify the Investigator in writing that samples have been destroyed.

14 CONDITIONS FOR MODIFYING THE PROTOCOL

If deemed necessary, protocol modifications will be prepared, reviewed, and approved by the Sponsor representatives.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (eg, change in monitor or change of telephone number).

15 CONDITIONS FOR TERMINATING THE STUDY

The study will be considered complete if any of the following criteria apply:

- futility analysis of PFS: the trial has been declared futile by the Sponsor, or
- primary analysis of PFS: null hypothesis is not rejected, or
- primary analysis of PFS: null hypothesis is rejected for PFS and the null hypothesis is rejected for OS (or the final planned analysis for OS has been conducted).

The Sponsor reserves the right to terminate the study, and Investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, the Sponsor and the Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

16 STUDY DOCUMENTATION, CASE REPORT FORMS, AND RECORD KEEPING

16.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the Investigator's study file and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subjects' clinical source documents to record key efficacy and safety parameters independent of the CRFs include the subjects' hospital/ clinic records; physician's and nurse's notes; the appointment book; original laboratory, ECG, electroencephalogram, x-ray, pathology and special assessment reports; signed ICFs; consultant letters; and subject screening and enrollment logs.

The Investigator must keep these two categories of documents on file for the maximum period required by applicable regulations and guidelines, institution procedures, or for the period specified by the Sponsor or designee, whichever is longer. After that period, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirements at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

16.2 Source Documents and Background Data

Upon request, the Investigator will make available for review to the Sponsor any required background data from the study documentation or clinic records. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

16.3 Audits and Inspections

The Investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Sponsor's Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

16.4 Case Report Forms

The term "case report form" (CRF) includes EDC screens or forms for studies that utilize EDC. For enrolled subjects, all and only data for the procedures and assessments specified in this protocol and required by the CRFs are to be submitted on the appropriate CRF (unless source data are transmitted to the Sponsor or a designee electronically, eg, central laboratory data). Data from some procedures required by the protocol, such as physical examinations, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the Investigator's institution or medical practice standard of care. Data from assessments associated with the follow-up of AEs are to be recorded on unscheduled CRF pages. Otherwise, data for unscheduled or additional assessments are to remain in the subject's medical record and are not to be recorded on CRFs unless specifically requested.

The CRF casebook must be completed and signed by the Investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study. If a `subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports.

The Sponsor's data management personnel (or designees) may, in specific circumstances, modify study data – without changing the meaning of the data – to ensure the dataset complies with conventions required for successful data extract, thesaurus coding, or uniform reporting and does not cause these processes to fail. Examples of these administrative changes include:

- Substitution of non-standard ASCII characters (codes 128-255) or deletion of carriage returns (code 13) that are incompatible with the SAS XPT file format (eg, accented letters replaced with non-accented ones; e for é)

- Splitting multiple verbatim AE terms into multiple records (eg, “nausea and vomiting” to separate records for “nausea” and “vomiting”)

- Reformatting failed eligibility criteria numbers for uniformity or specificity (eg, changing “2 a” to “2A”; or “2” to “2A” based on corroborating evidence from the clinical database)

- Changing cause of death from “unknown” to “unknown cause of death” to facilitate coding in the MedDRA thesaurus

Such changes follow a pre-defined documented process and can be clearly identified in the database audit trial. By participating in this study, investigators agree that such administrative changes are permissible without their specific prior approval. A list of all specific changes made can be provided to investigators upon request at any time.

17 MONITORING THE STUDY

The responsible Sponsor monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (CRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor’s responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor is to have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

18 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor or designees, subjects are to be identified by identification codes and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator must maintain documents not for submission to the Sponsor or designees (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to the Sponsor and its partners or designees for review.

19 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In the event that the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of the Investigator(s) or other representatives of the study site(s) as named author(s) shall be determined in accordance with Sponsor policy. Authorship will be assigned in accordance with contribution to design, execution, and interpretation and analysis of the study.

The Sponsor may, at its sole option, provide funding to support the development, submission, and/or presentation of publications for scientific/medical journals or conferences. For publications coordinated by the Sponsor, the Sponsor may also provide funding to support travel and conference registration for the presenting author to attend the conference for the sole purpose of presenting the publication.

20 COMPLIANCE WITH DATA PROTECTION LAWS

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation ((EU) 2016/679) and any national implementing laws, regulations and secondary legislation, as amended or updated from time to time. Sponsor shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law (which may include consent from the subject or another lawful basis).

21 REFERENCES

Albiges L, Tannir NM, Burotto M, McDermott DF, Plimack ER, Barthélémy P, Porta C, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma in CheckMate 214: 4-year follow-up and subgroup analysis of patients without nephrectomy. Ann Oncol. 2020;31 (Suppl 4):S559–S560. Abstract 711P.

Apolo AB, Mortazavi A, Stein M, Pal SK, Davarpanah N, Parnes HL, et al. A phase I study of cabozantinib plus nivolumab (CaboNivo) in patients (pts) refractory metastatic urothelial carcinoma (mUC) and other genitourinary tumors. Ann Oncol. 2016;27(suppl 6). Abstract 774PD.

Apolo AB, Tomita Y, Lee M-J, Lee S, Frosch A, Steinberg SM, et al. Effect of cabozantinib on immunosuppressive subsets in metastatic urothelial carcinoma. J Clin Oncol. 2014;32(suppl_15). Abstract 4501.

Banumathy G, Cairns P. Signaling pathways in renal cell carcinoma. Cancer Biol Ther. 2010;10(7):658-64.

Choueiri TK, Powles T, Burotto M, Bourlon MT, Zurawski B, et al. Nivolumab + cabozantinib vs sunitinb in first-line treatment for advanced renal cell carcinoma: First results from the randomized Phase III CheckMate 9ER trial. Ann Oncol. 2020;31 (Suppl 4):S1159. Abstract 6960_PR.

Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018;94:115-125.

Choueiri TK, Hessel C, Halabi S, Sanford B, Hahn O, Michaelson MD, et al. Progression-free survival by independent review and updated overall survival results from Alliance A031203 trial (CABOSUN): cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma. Ann Oncol. 2017;28(suppl_5). Abstract LBA38.

Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-27.

Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1814-23.

Ciamporcero E, Miles KM, Adelaiye R, Ramakrishnan S, Shen L, Ku S, Pizzimenti S, et al. Combination strategy targeting VEGF and HGF/c-met in human renal cell carcinoma models. Mol Cancer Ther. 2015;14(1):101-10.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Published: November 27, 2017 [cited 30 April 2018]. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31:3639-46.

Escudier B, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, et al. CheckMate 025 randomized Phase 3 study: Outcomes by key baseline factors and prior therapy for nivolumab versus everolimus in advanced renal cell carcinoma. Eur Urol. 2017;72(6):962-971.

FDA. Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. December 2018.

Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol. 2007;102(9):2086-102.

Gibney GT1, Aziz SA, Camp RL, Conrad P, Schwartz BE, Chen CR, et al. c-Met is a prognostic marker and potential therapeutic target in clear cell renal cell carcinoma. Ann Oncol. 2013;24(2):343-9.

Hammers HJ, Plimack ER, Infante JR, Rini BI, McDermott DF, Lewis LD, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 Study. J Clin Oncol. 2017;35(34):3851-3858.

Herbst RS, Earon E, Kim D-W, Cho BC, Gadgeal S, Léna H et al. KEYNOTE-010: Durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. J Thor Oncol 2016; 12(1_suppl). Abstract 0A03.07.

Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141-8.

Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794-9.

Hessel C, Mangeshkar M, Motzer RJ, Escudier B, Powles TB, Schwab G, Choueiri TK. Evaluation of the novel "trial within a trial" design of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced RCC. Ann Oncol. 2016;27(6):266-95. Abstract 8158.

Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006 Sep 20;98(18):1331-4.

Kwilas AR, Ardiani A, Donahue RN, Aftab DT, Hodge JW. Dual effects of a targeted small-molecule inhibitor (cabozantinib) on immune-mediated killing of tumor cells and immune tumor microenvironment permissiveness when combined with a cancer vaccine. J Transl Med. 2014;12:294.

Lu X, Horner JW, Paul E, Shang X, Troncoso P, Deng P, et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. Nature. 2017;543(7647):728-32.

Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139-48.

Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019;20(10):1370-1385.

Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-90.

Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1803-13.

Nadal RM, Mortazavi A, Stein M, Pal SK, Davarpanah NN, Parnes HL et al. Results of phase I plus expansion cohorts of cabozantinib (Cabo) plus nivolumab (Nivo) and CaboNivo plus ipilimumab (Ipi) in patients (pts) with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies. J Clin Oncol. 2018;36(suppl 6). Abstract 515.

Nadal R, Mortazavi A, Stein M, Pal SK, Davarpanah N, Parnes H, et al. Final results of a Phase I study of cabozantinib + nivolumab and cabozantinib + nivolumab + ipilimumab in patients with metastatic urothelial carcinoma and other genitourinary malignancies. Ann Oncol. 2017;28:(suppl 5):v295-v329. Abstract 8460.

NCCN. National Comprehensive Cancer Network Guidelines. Kidney Cancer. Version 3.2018. February 6, 2018.

Robert C, Long G, Schachter J, Arance A, Grob J, Mortier L, et al. Long-term outcomes in patients with ipilimumab-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab treatment; Journal of Clinical Oncology 2017 35:(15_suppl). Abstract 9504.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.

Song EK, Tai WM, Messersmith WA, Bagby S, Purkey A, Quackenbush KS, et al. Potent antitumor activity of cabozantinib, a c-MET and VEGFR2 inhibitor, in a colorectal cancer patient-derived tumor explant model. Int J Cancer. 2015;136(8):1967-75.

Spigel DR, McLeod M, Hussein M, Waterhouse D, Einhorn L, Horn L, et al. Randomized results of fixed-duration (1-year) vs continuous nivolumab in patients with advanced non-small cell lung cancer. Ann Oncol. 2017;28(Suppl_5). Abstract 12970.

Sun M, Shariat SF, Cheng C, Ficarra V, Murai M, Oudard S, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol. 2011;60(4):644-61.

Tolaney SM, Ziehr DR, Guo H, Ng MR, Barry WT, Higgins MJ, et al. Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients. Oncologist. 2017 Jan;22(1):25-32.

Turnage RH, Badgwell B. Abdominal wall, umbilicus, peritoenum, mesentery, omentum and retroperitoneum. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston Textbook of Surgery. 19th ed. Philadelphia, PA: Saunders Elsevier; 2012. p1102.

Wright JR, Ung YC, Julian JA, Pritchard KI, Whelan TJ, Smith C, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007;25(9):1027-32.

Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother. 2007;30(8):825-30.

Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015;67(3):519-30.

Zhou L, Liu XD, Sun M, Zhang X, German P, Bai S, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016;35(21):2687-97.

APPENDICES

Appendix A: Schedule of Assessments

The schedule of required assessments is presented in this appendix. Following randomization, assessments for safety and patient reported outcomes are to occur corresponding with study weeks (eg, Week 3 Day 1 [W3D1]), which are fixed from Week 1 Day 1 (W1D1), defined as the date of the first dose of study treatment. W1D1 should occur within 3 days after randomization. All assessments for radiographic endpoints (CT, MRI, bone scans) as well as EQ-5D-5L will be scheduled based on the date of randomization and are to be performed even for subjects randomized but never treated. For such subjects, W1D1 is defined as the date of randomization. In the absence of toxicity, all scheduled safety visits should occur within ± 3 days of the nominal time through W14D1 and within ± 5 days of the nominal visit day after W14D1, unless otherwise indicated. If study treatment is held or missed after W1D1, assessments should continue following the schedule described below.

Unscheduled safety assessments, if required as defined in the protocol, are to be performed weekly (or more frequently as clinically indicated). See Section 5.5 for further details.

Special accommodations during the global COVID-19 pandemic are described in Appendix K.

Appendix A: Schedule of Assessments

	Pre-randomization	Post-randomization											
			(± 3 Days)										
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W 3 D 1**	**W 4 D 1**	**W 6 D 1**	**W 7 D 1**	**W 9 D 1**	**W 10 D 1**	**W 12 D 1**	**W 14 D 1**	**After Beginning of Week 14 (± 5 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)[m]**	**Second Follow-Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)[m]**
Informed consent (Section 5.1)	X[b]												
Demographics, medical and cancer history (Section 5.7.1)	≤ 28 days	X											
Physical examination + weight (Section 5.7.2)	≤ 14 days (with height)	X (prior to first dose; symptom-directed)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
Vital signs (Section 5.7.3)	≤ 14 days	X (prior to first dose)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
IMDC prognostic score (Section 3.4)	≤ 14 days												
Karnofsky performance status (Section 5.7.2)	≤ 14 days	X (prior to first dose)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
12-lead ECG (Section 5.7.4)[c]	≤ 14 days	X[d] (prior to first dose)				X				X	Every 12 weeks (W26D1, W38D1, etc)	X	
Hematology[e] (Section 5.7.5)	≤14 days	X[d] (prior to first dose)	X	X	X	X	X	X	X	X	Every 4 weeks (W18D1, W22D1, etc)	X	
Serum chemistry[e] (Section 5.7.5)	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	X	X	X	X	Every 4 weeks (W18D1, W22D1, etc)	X	

Appendix A: Schedule of Assessments (continued)

	Pre-randomization	Post-randomization											
			(± 3 Days)										
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W 3 D 1**	**W 4 D 1**	**W 6 D 1**	**W 7 D 1**	**W 9 D 1**	**W 10 D 1**	**W 12 D 1**	**W 14 D 1**	**After Beginning of Week 14 (± 5 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)[m]**	**Second Follow-Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)[m]**
PT/INR and PTT (Section 5.7.5)	≤ 14 days	X[d] (prior to first dose)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
Thyroid function test (Section 5.7.5)	≤ 14 days			X		X		X		X	Every 8 weeks (W22D1, W30D1, etc)	X	
Follicle stimulating hormone [f] (Section 5.7.5)	≤ 14 days												
Hepatitis screening[g] (Section 5.7.5)	≤ 14 days												
HIV testing (if required by local regulations; Section 5.7.5)	≤ 14 days												
UPCR (Section 5.7.5). (In addition, 24-h urine protein by **local** lab at Investigator's discretion.)	≤ 14 days	X[d] (prior to first dose)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
Urinalysis by **local** lab[e] (Section 5.7.5)	≤ 14 days	X[d] (prior to first dose)	X	X	X	X	X	X	X	X	Every 4 weeks (W18D1, W22D1, etc)	X	
Serum or urine pregnancy test by **local** lab[e] (Section 5.7.5)	≤ 7 days (serum)	X[d] (serum: prior to first dose)		X		X		X		X	Every 4 weeks (W18D1, W22D1, etc)	X	
Tumor tissue (Section 5.7.11)	X[h]					X[l]							

Appendix A: Schedule of Assessments (continued)

	Pre-randomization	Post-randomization										
			(± 3 Days)									
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W 3 D 1**	**W 4 D 1**	**W 6 D 1**	**W 7 D 1**	**W 9 D 1**	**W 10 D 1**	**W 12 D 1**	**W 14 D 1**	**After Beginning of Week 14 (± 5 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)[m]**	**Second Follow-Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)[m]**
Tumor assessment: CT/MRI **Chest, Abdomen, Pelvis** (Section 5.7.6)	≤ 28 days	CT of CAP or CT chest and MRI of abdomen/pelvis will be performed in all subjects at screening, at W10D1 (± 7 days), and every 8 weeks (± 7 days) after randomization through Week 50. After Week 50, these assessments will be performed every 12 weeks (± 7 days). Tumor assessments should continue on the protocol-defined schedule, relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued. The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization. For subjects who discontinue study treatment before Investigator-assessed radiographic PD, tumor assessments are to continue per the protocol defined schedule until Investigator-assessed radiographic PD per RECIST 1.1. For subjects who continue to receive study treatment after investigator-assessed radiographic PD because of investigator-assessed clinical benefit that outweighs the potential risks, tumor assessments are to continue per the protocol defined schedule until study treatment is permanently discontinued.											
Tumor assessment: MRI/CT **Brain** (Section 5.7.6)	≤ 28 days	MRI (or CT) of the brain will be performed at screening in all subjects at screening. After randomization, MRI (or CT) scans of the brain are only required in subjects with known brain metastasis or if clinically indicated by signs and symptoms suggestive of new central nervous system (CNS) metastases. Assessments after randomization will be performed at the same frequency as imaging for CAP. MRI is the preferred method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI unless MRI is contraindicated. Tumor assessments should continue on the protocol-defined schedule, relative to the date of randomization, regardless of whether study treatment is given, reduced, held or discontinued. The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization. For subjects who discontinue study treatment before Investigator-assessed radiographic PD, tumor assessments are to continue per the protocol defined schedule until Investigator-assessed radiographic PD per RECIST 1.1. For subjects who continue to receive study treatment after investigator-assessed radiographic PD because of investigator-assessed clinical benefit that outweighs the potential risks, tumor assessments are to continue per the protocol defined schedule until study treatment is permanently discontinued.											
Tumor assessment: Bone scan **Whole body** (Section 5.7.6)	≤ 28 days	Technetium bone scans should be performed at screening for all subjects. After randomization, bone scans will be performed in subjects with known bone metastases and otherwise as clinically indicated per standard of care. Any soft tissue lesions associated with identified bone lesions must be imaged by CT/MRI and assessed in alignment with the CAP assessments. Bone scan findings alone cannot be used for the determination of progression or response and need to be corroborated by CT or MRI (which will be used as the basis for RECIST evaluations).										

Appendix A: Schedule of Assessments (continued)

	Pre-randomization	Post-randomization											
			(± 3 Days)										
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W 3 D 1**	**W 4 D 1**	**W 6 D 1**	**W 7 D 1**	**W 9 D 1**	**W 10 D 1**	**W 12 D 1**	**W 14 D 1**	**After Beginning of Week 14 (± 5 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)[m]**	**Second Follow-Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)[m]**
HRQOL- EQ-5D-5L[i] (Section 5.7.7)	≤ 14 days		W4D1, W7D1, W10D1, W14D1 then every 4 weeks thereafter. These assessments are to be performed regardless of whether study treatment is given, reduced, held or discontinued until the date of the last tumor imaging assessment as described in Section 5.7.6. Consequently these assessments may be required in the Post Treatment Period for some subjects.										
Health Care Resource Utilization (Section 5.7.8)		Hospital admissions, emergency room visits, intensive care unit admissions, surgeries, and transfusions from randomization through the FU-2 visit.											
Cabozantinib/placebo PK plasma samples[j,k] (Section 5.7.9)		X (prior to first dose)		X		X		X		X			
Nivolumab+ipilimumab PK serum samples[k] (Section 5.7.9)		X (prior to first dose)		X		X		X		X	W26D1	X	X
Immunogenicity blood sample[k] (Section 5.7.10)		X (prior to first dose)								X	W26D1	X	X
Pharmacogenetic blood sample[k] (Section 5.7.11)		X (prior to first dose)											
Immune cell profiling blood sample[k] (Section 5.7.11)		X (prior to first dose)				X				X			
Plasma biomarker samples[k] (Section 5.7.11)		X (prior to first dose)		X		X		X		X		X	
Cell and/or pharmacogenomic blood sample[k] (Section 5.7.11)		X (prior to first dose)				X				X		X	
Concomitant medication (Section 7)	Document concomitant medication taken from 28 days before randomization through 30 days after the date of the decision to discontinue study treatment												

Appendix A: Schedule of Assessments (continued)

	Pre-randomization	Post-randomization										
			(± 3 Days)									
Assessment:	**Screening[a] (before randomization)**	**W1D1 (≤ 3 days after randomization)**	**W 3 D 1**	**W 4 D 1**	**W 6 D 1**	**W 7 D 1**	**W 9 D 1**	**W 10 D 1**	**W 12 D 1**	**W 14 D 1**	**After Beginning of Week 14 (± 5 days)**	**First Post-Treatment Follow-Up Visit (FU-1; 30+14 days after decision to discontinue study treatment)[m]**	**Second Follow-Up Visit (FU-2; 100±14 days after decision to discontinue study treatment)[m]**
Adverse events (Section 8)	Document new or worsening AEs from informed consent for SAEs and from first dose for nonserious AEs. Continue monitoring through 30 days (100 days for unrelated SAEs [Table 8-1]) after the date of the decision to permanently discontinue study treatment. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. On W1D1 AEs will be documented pre- and post-dose. Related AEs leading to study treatment discontinuation, AESIs (regardless of causality), and related SAEs are to be followed until resolution, ≤ Grade 2 severity, or determination by the Investigator that the event is stable or irreversible (see Section 8.3).											
Cabozantinib / Placebo dosing (Section 6.1.1.1 / 6.1.1.2)		Cabozantinib or placebo tablets given on W1D1 after nivolumab/ipilimumab infusion. Taken once daily at home thereafter until study treatment is discontinued.										
Nivolumab dosing (Section 6.1.1.3; weight-based dose W1D1, W4D1, W7D1, W10D1, flat dose from W14D1 onwards)		X		X		X		X		Nivolumab will be administered as an IV infusion at the clinic W14D1 and every 4 weeks until treatment is discontinued (to a maximum of 2 years).		
Ipilimumab dosing (Section 6.1.1.3; weight-based dose W1D1, W4D1, W7D1, W10D1)		X		X		X		X	No further doses			
Dispense/return of oral study drug and compliance accounting (Section 6.5)[n]		X		X		X		X		X	Every 4 weeks (W18D1, W22D1 etc)		
Additional systemic anti-cancer treatment and survival status (Sections 5.7.12)		All treated subjects will be contacted at each post-treatment visit, including FU-1, FU-2, and every 12 weeks (+ 14 days) after FU-2 visit until death. Any subjects who are randomized but not treated will be contacted every 12 weeks post-randomization until death.										

[a] Results of screening assessments must be reviewed before randomization to confirm that the subject meets the eligibility criteria.

[b] Informed consent may be obtained greater than 28 days prior to randomization but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by the site's IRB/EC policies.

[c] Additional ECGs should be performed if clinically indicated.

[d] This assessment is intended to confirm suitability for treatment after randomization. If this assessment has been performed during screening within 14 days (7 days for pregnancy test for females of child-bearing potential) prior to first dose (W1D1), this assessment does not need to be performed on W1D1 unless the subject's clinical status has changed (eg, onset of new symptoms indicative of clinical deterioration). If the assessment is performed on W1D1, the results must be available to and reviewed by the Investigator prior to any treatment being administered.

[e] Serum chemistry, hematology, and urinalysis laboratory samples must be collected within 72 hours and the results be reviewed before any study treatment infusion administered on study. These assessments are not required prior to the first dose if there has been no change in subject's clinical status since screening. Results (with the exception of routine urinalyses and pregnancy tests) must be provided to the local laboratory management vendor. See Section 5.7.5 and the Laboratory Manual for more detailed information on laboratory assessments.

[f] For women under the age of 55 years, confirm menopause as needed.

[g] Hepatitis B surface antigen and Hepatitis C antibody (with reflex testing of HCV RNA if antibody test is positive) to be assessed at screening.

[h] Shipment of archival tumor tissue (unstained slides or paraffin block) to the study central laboratory prior to randomization. The tissue can be obtained/sampled from any organ except brain or bone and must be biopsied no more than 2 years prior to the date of informed consent. Alternatively, a fresh tumor sample must be obtained and shipped to the study central laboratory prior to randomization if archival tissue is unavailable or inadequate.

[i] HRQOL forms should be administered and collected prior to any other study-related activities for scheduled visits. Questionnaires should be completed prior to the clinic visit.

[j] For each on-treatment visit, the PK sample should be collected approximately 8 or more hours after the previous dose of cabozantinib/placebo, and if cabozantinib/placebo will be administered on that day, should be collected prior to cabozantinib/placebo administration. The investigator will ask the subject for the date and time of the most recent prior dose of cabozantinib/placebo and this information will be recorded on the appropriate CRF page.

[k] Central laboratory assessements are required for these measurements.

[l] An optional biopsy can be collected approximately 6 weeks after the first dose of study treatment.

[m] Date of the decision to permanently discontinue study treatment by the subject is defined as the later of the decision to permanently discontinue study treatment or the last dose of study treatment.

[n] In exceptional circumstances (eg, COVID-19 pandemic), alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations.

Appendix B: Maintenance Phase

When sufficient data have been collected to adequately evaluate all study endpoints, and after treatment assignment has been unblinded, the Sponsor may initiate a Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established for regulatory purposes. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).

In the Maintenance Phase subjects will continue to receive active study treatment until a criterion for protocol-defined discontinuation has been met (Section 3.6.1). Subjects in the Maintenance Phase are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per institutional standard of care and guidance from the Sponsor as necessary. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.

In order to continue to collect important safety information on subjects still enrolled in the study, reporting of SAEs, AESIs, and other reportable events (pregnancy, DILI and medication errors with sequelae) is to continue per protocol (Section 8.2).

Further, the following events (whether serious or not) are to be reported using the same process as for reporting SAEs described in protocol Section 8.2 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse events of special interest (AESIs)
- Adverse events, whether serious or not, leading to study treatment discontinuation
- Adverse events, whether serious or not, leading to study treatment dose modification (ie, causing study treatment to be interrupted, delayed, or reduced)

Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2) at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the Post-Treatment Follow-up Visits. Upon initiation of the Maintenance Phase, no further follow up is required for any subject who has completed the FU-1 and FU-2 Visits.

Study drug accountability is to continue as described in Section 6.5.

See the Maintenance Phase Schedule of Assessments below. To receive study treatment supplies it may be necessary for subjects to visit the study site more frequently than clinic visits for safety and tumor evaluations performed per standard of care.

Site monitoring visits will occur at a reduced frequency but must be frequent enough to ensure adherence to GCP, protocol compliance, adequate subject safety follow-up, study drug accountability, and reporting of SAEs and other reportable events.

During the Maintenance Phase no data are to be entered into CRFs. Study central laboratory samples are not to be obtained. Local laboratory results are not to be submitted to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central ECG vendor.

Schedule of Assessments: Maintenance Phase

Assessment	Study Period / Visit	
	While Subject is Receiving Study Treatment (Until Treatment is Permanently Discontinued)	**Post-Treatment Follow-Up Visits (ie, FU-1 and FU-2)**
Study drug accountability	Every time study drug is dispensed	✓[a]
Study treatment	Nivolumab infusion: Once every 4 weeks (maximum of 2 years of treatment in total); Cabozantinib (oral): Daily. Study treatment may continue until a criterion for discontinuation is met (Section 3.6.1).	-
Safety evaluation: *Clinical examination and local laboratory assessments per SOC*	Frequency per standard of care	✓[a]
Reporting of SAEs, AESIs, and other reportable events (DILI, pregnancy, medication errors with sequelae)	Submit reports to Sponsor per Section 8.2	
Reporting of AEs (including AESIs): • leading to study treatment discontinuation • leading to study treatment dose modification (ie, causing study treatment to be withheld or reduced)	Submit reports to Sponsor per the same process as for reporting SAEs per Section 8.2 SAE reporting timeline requirements do not apply to non-serious events reported in these categories	
Tumor assessments: *Imaging methods per SOC*	Frequency per standard of care	-

AE, adverse event; DILI, drug-induced liver injury; FU-1, 30-Day Post-Treatment Follow-up Visit; FU-2, 100-Day Post-Treatment Follow-up Visit; SAE, serious adverse event; SOC; standard of care
No data will be entered into electronic case report forms. Do not submit local laboratory results to the study local laboratory management vendor, radiographic images to the study central imaging vendor, or ECGs to the study central ECG vendor.
[a] Subjects should return all unused study medication and undergo a safety evaluation per standard of care.

Appendix C: Karnofsky Performance Status Criteria

ECOG Performance Status Scale (reference only)		Karnofsky Performance Status Scale	
Grade	**Description**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix D: Highly Effective Methods of Contraception

In Inclusion Criterion #10 (Section 4.2), sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly during the course of the study and until the end of relevant systemic exposure, defined as 5 months for women, and 7 months for men, after the last dose of study treatment.

The effect of cabozantinib on the PK of contraceptive steroids has not been investigated. Because oral contraceptives might possibly not be considered as "effective methods of contraception," they should be used together with another method.

Contraception guidance for female subjects of childbearing potential

One of the highly effective methods of contraception listed below, in combination with one acceptable barrier method below, is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the last dose of study treatment. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly effective contraceptive methods that are user dependent: These methods have a failure rate of < 1% per year when used consistently and correctly. 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.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral or injectable

Highly effective contraceptive methods that are user independent:

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation

- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system
- Intrauterine device
- 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 female subject of childbearing potential 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.
        - Female subjects of childbearing potential who choose complete abstinence must continue to have pregnancy tests per the protocol. Acceptable alternate methods of highly effective contraception must be discussed in the event that any of these subjects chooses to forego complete abstinence.

Acceptable barrier methods for use in combination with a highly effective method:

- Male or female condom with or without spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide

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 of which inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods)
- Withdrawal (eg, coitus interruptus).
- Spermicide only
- Lactation amenorrhea method

Contraception guidance for male participants with partner(s) of childbearing potential

Male subjects with female partners of childbearing potential are eligible if they agree to the following during the treatment and until the end of relevant systemic exposure, defined as 7 months after the last dose of study treatment.

- 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 subjects are required to use a condom during study duration and until end of relevant systemic exposure, defined as 7 months after the last dose of study treatment.
- Female partners of male subjects in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the last dose of treatment in the male participant.

Male subjects 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 last dose of study treatment. Refrain from donating sperm for the duration of the study treatment and until 7 months after the last dose of study treatment.

Appendix E: Management Algorithms

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

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

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

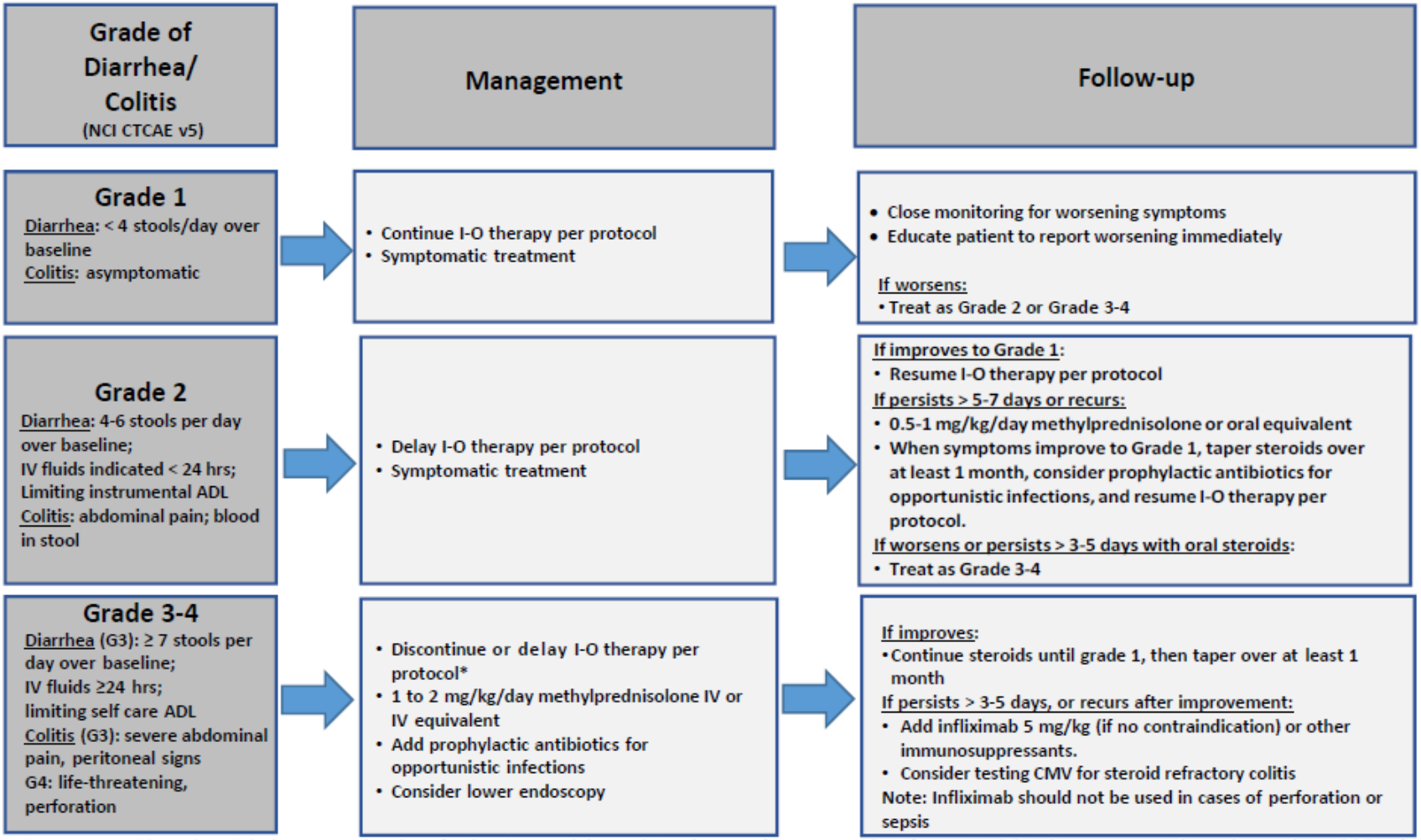
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

For recommendations on dose modifications of BOTH cabozantinib/placebo treatment and nivolumab/ipilimumab treatment due to hepatocellular toxicity, see Section 6.6.1.

GI Adverse Event Management Algorithm

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

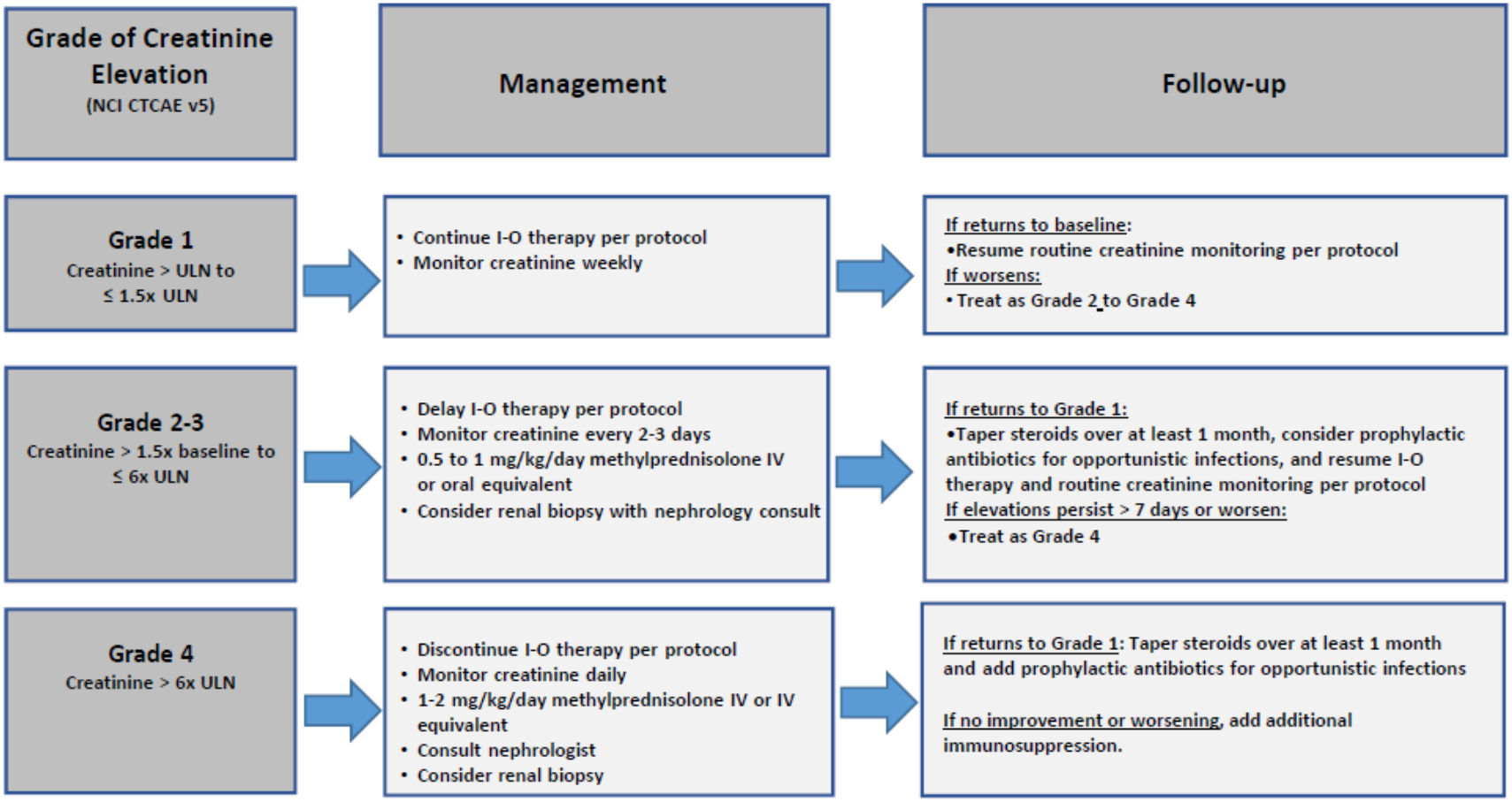


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

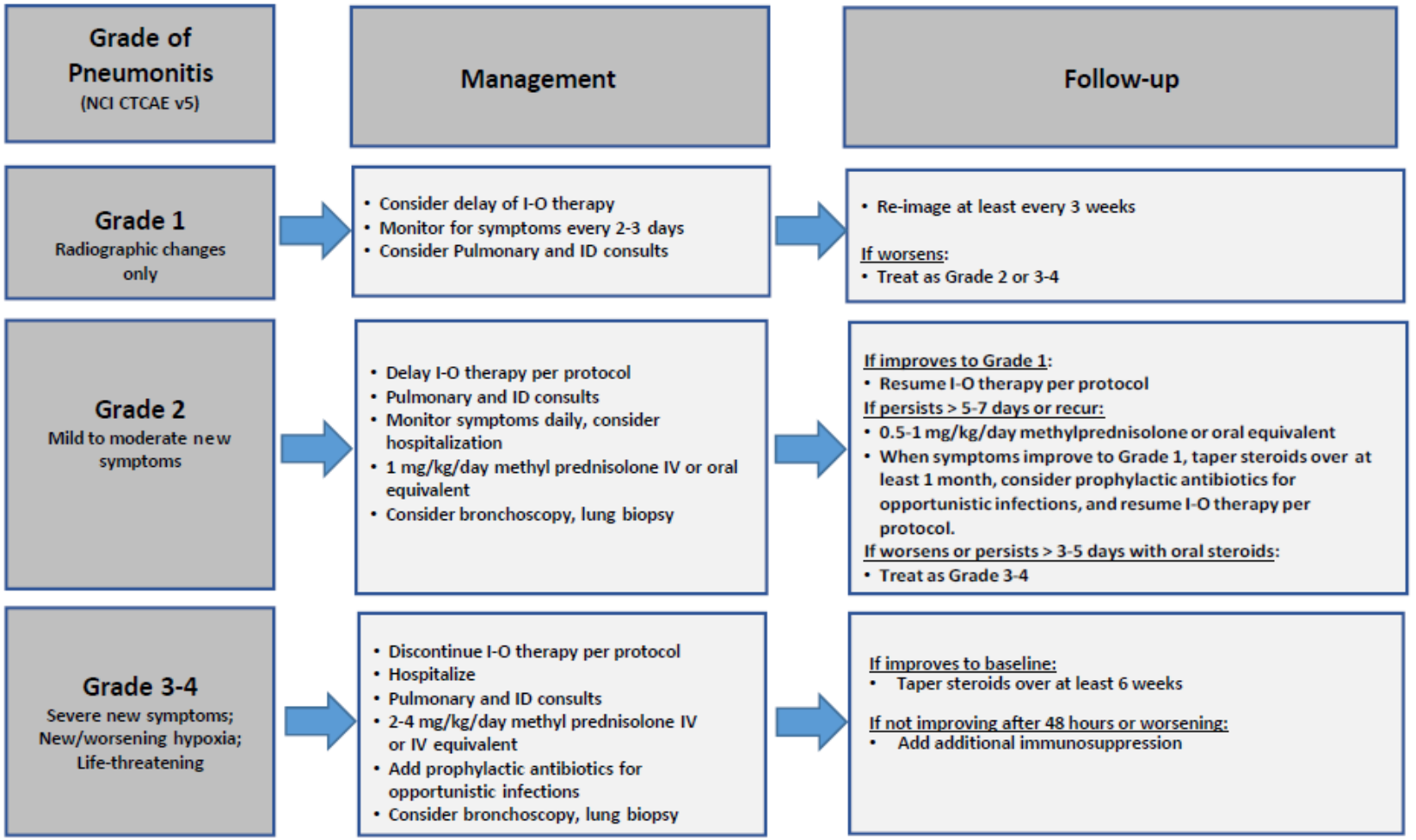
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

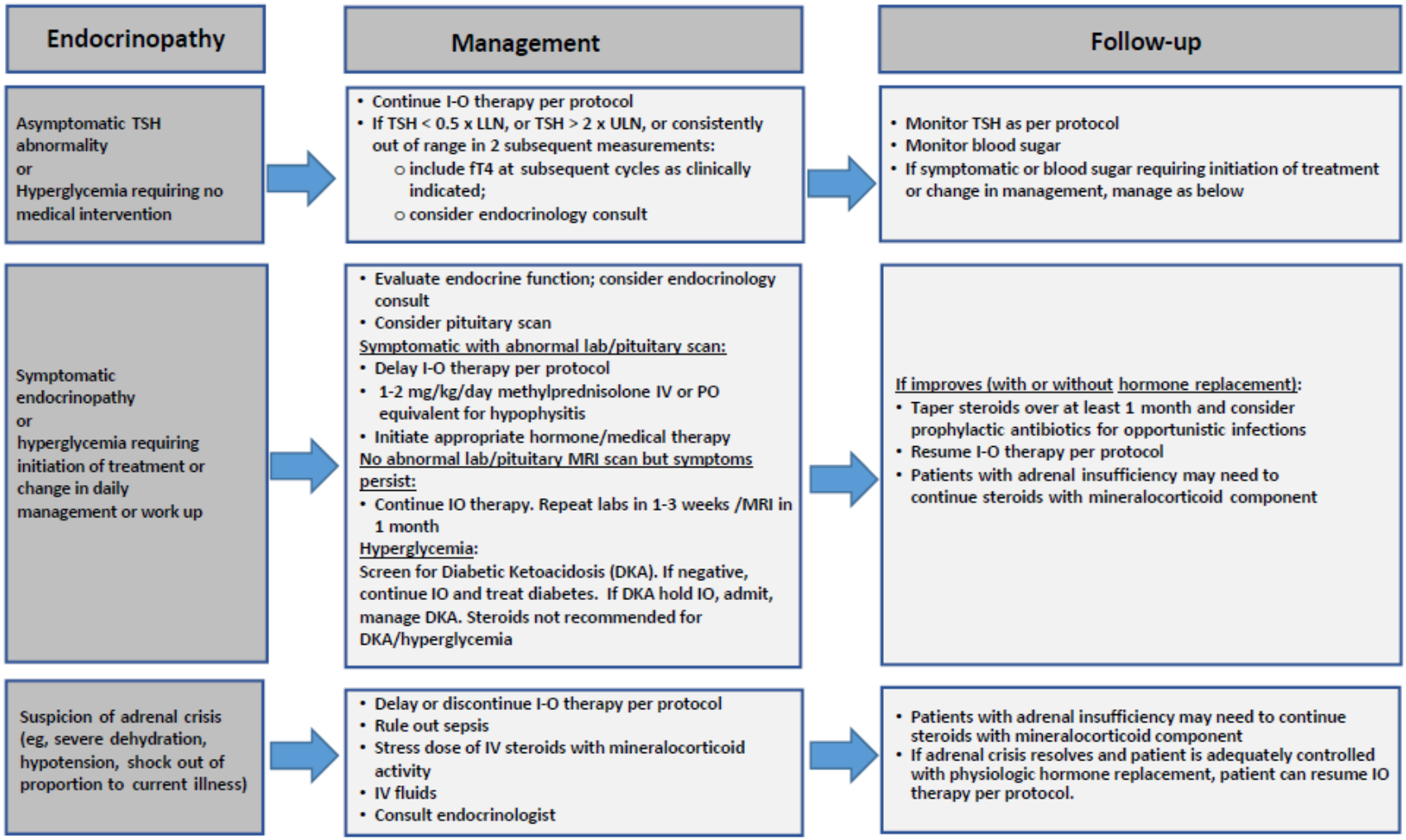
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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

Endocrinopathy Adverse Event Management Algorithm

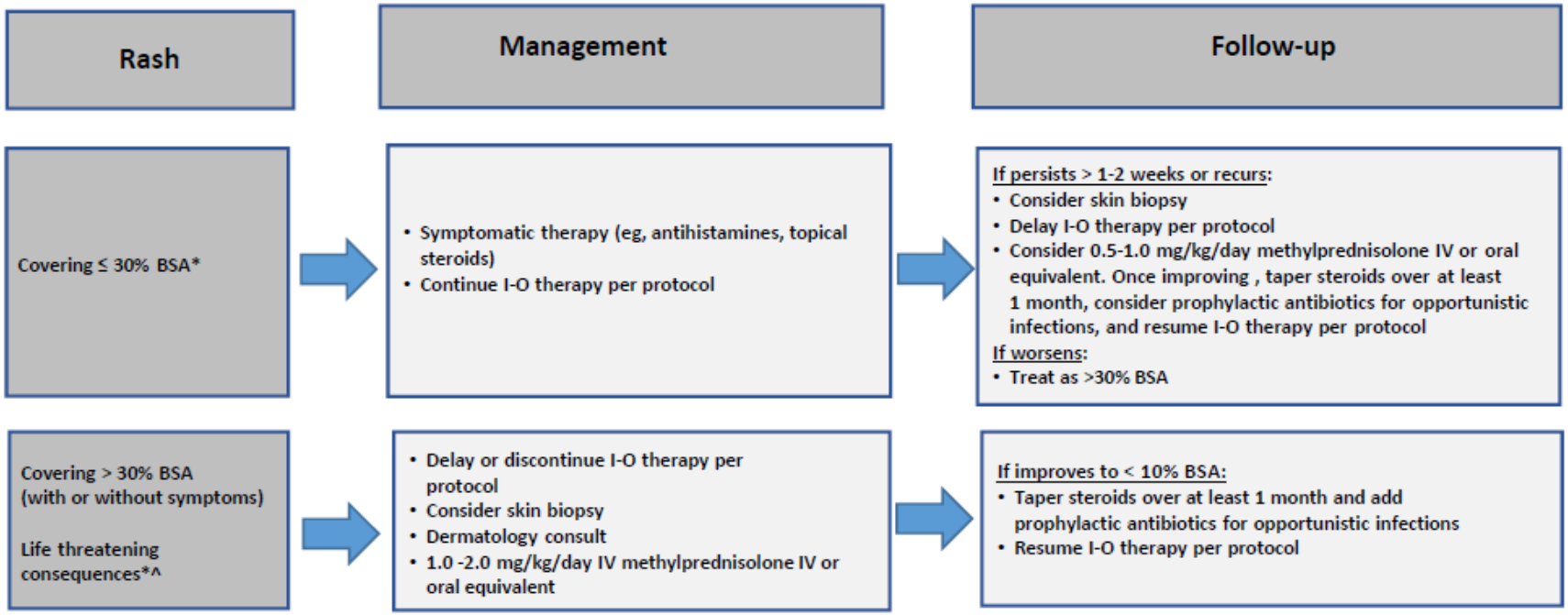
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



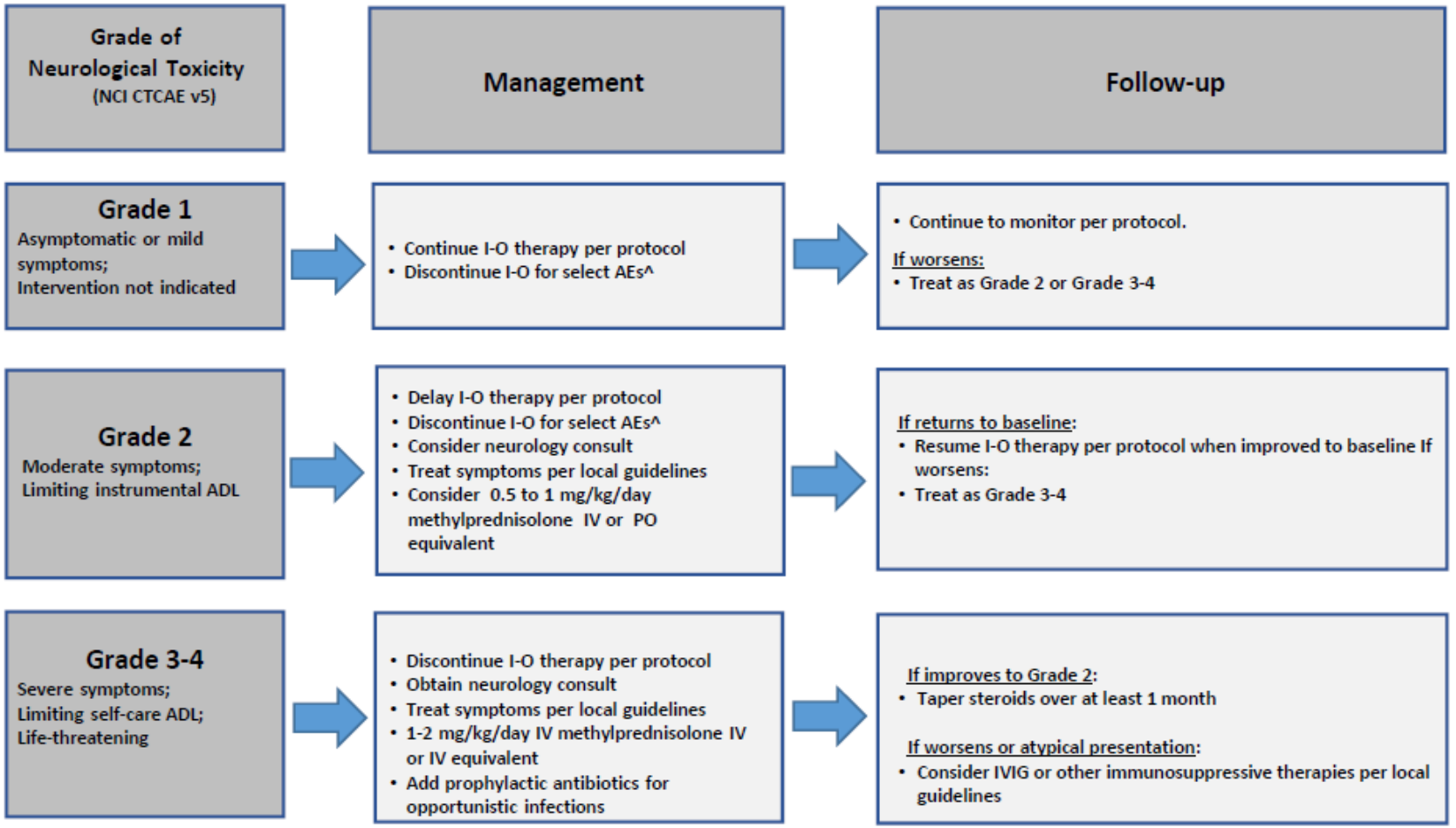
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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

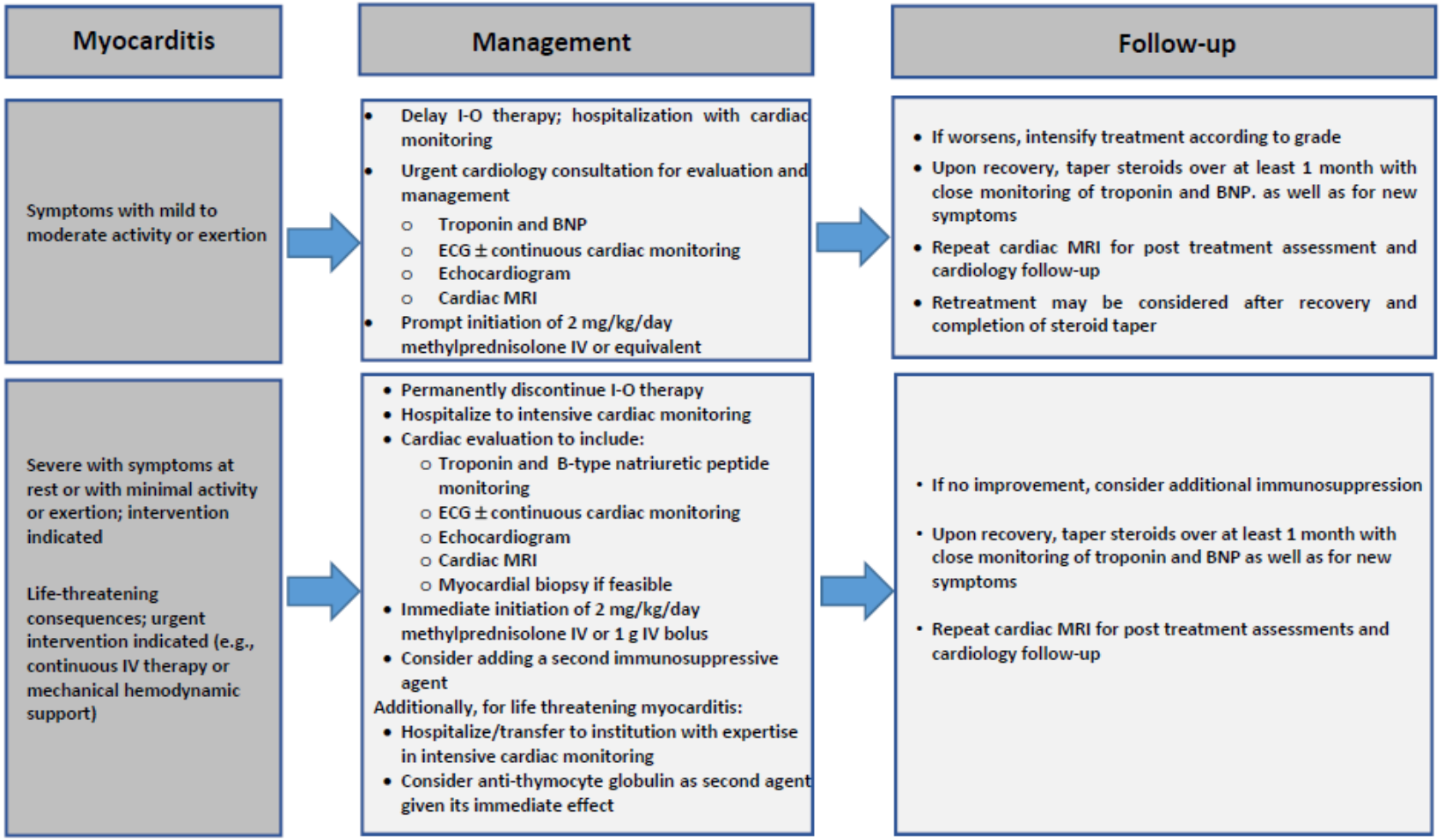


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis Adverse Event Management Algorithm

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



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

Appendix F: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

Adapted from Eisenhauer et al 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- 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 recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis < 10 mm are considered nonpathological and are not be recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable. Following a timepoint response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with

the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are generally not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed. Following a timepoint response of CR, non-target lymph node lesions and new lymph node lesions must be measured to determine if they are or become pathologic in size.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic 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 noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be

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

- Blastic bone lesions are non-measurable.

Lesions with prior local treatment

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scan) except for lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Positron emission tomography will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study.

Bone scans may be used to assess the presence or disappearance of the bone component of bone lesions. CT or MRI scan will be used to confirm results of bone scans. Preferred method for confirmation is MRI.

Tumor Markers: Tumor markers may be evaluated for changes but will not be used to determine progressive disease in this study.

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is reduced, interrupted, delayed, or discontinued.

At baseline, tumors and lymph nodes are classified and documented as target or nontarget lesions per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple liver metastases'). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' should be included in source documents.

For target lesions, measurements should be taken and recorded in metric notation.

Nontarget lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a 'new' cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

Time point progression cannot be based solely on bone scan findings. Bone scans are to be used to direct corroborative imaging with CT/MRI if necessary. These CT/MRI findings will be used for the determination of progression.

TIME POINT RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD, baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions).

If the target lesion for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR / Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should normally not trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (NA)	No non-target lesions identified at screening.
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). Note: The appearance of one or more new lesions on CT or MRI scan is considered progression if these findings are unequivocally not due to a change in the imaging technique or modality. On bone scan, new lesions are not sufficient to qualify as PD. Confirmation should be obtained by performing CT or MRI of the area of concern to confirm results of bone scan. Preferred method for confirmation is MRI.
No	No new lesions present at follow-up.
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions.

Evaluation of Overall Time Point Response			
Target Lesion TPR	**Non-target lesion TPR**	**New lesion TPR**	**Overall TPR**
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Any except PD	No	UE
PD	Any	No or Yes	PD
Any	PD	No or Yes	PD
Any	Any	Yes	PD**
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE	No	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior or subsequent time point (ie, confirmation requirement isnot considered when assigning time point responses).

* Subjects with an overall response of CR or PR must have a follow-up tumor assessment performed no less than 4 weeks after the criteria for response are first met (this may be performed at the next scheduled tumor assessment). However, the presence, absence, or status at this follow up assessment is not considered when assigning a time point response at prior time points.

** If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the subject's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the subject's tumor had reached a CR status and the lesion reappeared, then the subject would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response.

Furthermore, in order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have a follow-up tumor assessment no later than the next scheduled tumor assessment. However, the presence, absence, or status at this follow up assessment is not considered when assigning a time point response at prior time points.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For subjects with an overall response of PR or CR at a given time point, a follow-up tumor assessment must be performed no less than 4 weeks after the criteria for response are first met. This may be performed at the next scheduled tumor assessment.

In order to identify potential delayed immune-mediated tumor response, subjects with an overall response of PD per RECIST 1.1 who continue with study treatment because of evidence of clinical benefit as assessed by the Investigator should have a follow-up tumor assessment no later than the next scheduled tumor assessment. However, the presence, absence, or status at these follow up assessments is not considered when assigning a time point response at prior time points.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

Appendix G: List of Strong Inducers and Inhibitors of CYP3A4

Cabozantinib is a CYP3A4 substrate (Section 7.3.1 Potential drug interactions with cabozantinib).

Chronic co-administration of cabozantinib with drugs known to be strong inducers of the CYP3A4 family may decrease cabozantinib concentrations and therefore should be avoided during treatment with cabozantinib. St. John's Wort (Hypericum perforatum) is also known to be an inducer of CYP3A4 and should be avoided.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family may increase cabozantinib concentrations and should be avoided during treatment with cabozantinib. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided during treatment with cabozantinib.

Strong Inhibitors of CYP3A4	Strong Inducers of CYPA4
Antivirals Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Indinavir Lopinavir Nelfinavir Ombitasvir Paritaprevir Ritonavir Saquinavir Telaprevir Tipranavir **Anti-Fungals** Itraconazole Ketoconazole Posaconazole Voriconazole **Antibiotics** Clarithromycin Telithromycin Troleandomycin Conivaptan Diltiazem Grapefruit juice/star fruit/Seville oranges Idelalisib Nefazodone	Carbamazepine Efavirenz Enzalutamide Erythromycin Mitotane Modafinil Nevirapine Oxcarbazepine Phenytoin Rifampin St. John's Wort

This table is not all-inclusive. Please refer to the FDA website for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Appendix H: Collection, Follow-Up, and Documentation Requirements for AEs, AESIs, and SAEs

All AEs that are not serious and not AESIs (AEs of special interest; see Table 8-1) that start or worsen after the first dose of study treatment through the 30-day post-treatment follow-up (FU-1) visit are to be entered into the electronic CRF data capture system (EDC). Such events continuing at the FU-1 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes. These events do not require a Drug Safety SAE Form to be completed.

Additional requirements apply to the following events:

- All SAEs that are judged by the investigator to be not related to study treatment that start or worsen after the subject's initial informed consent through the 100-day post-treatment follow-up (FU-2) visit are to have a Drug Safety SAE Form completed. Such events continuing at the FU-2 visit are to be documented as "ongoing" in the EDC and do not require further documentation for study purposes.

- All AEs leading to study treatment discontinuation that are judged by the Investigator to be related to study treatment and that are continuing at the FU-2 visit are to be followed by the Investigator until resolution, defined as fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required. If serious, the requirements for related SAEs apply.

- All AESIs (regardless of seriousness) that start or worsen after the subject's initial informed consent through the FU-2 visit are to have a Drug Safety SAE Form completed and be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution (as defined above), with evidence of resolution provided on updates to the Drug Safety SAE Form. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.

- All SAEs that are judged by the Investigator to be related to study treatment that start or worsen at any time after the subject's initial informed consent are to have a Drug Safety SAE Form completed. Such events that occur prior to the FU-2 visit are to be entered into the EDC. Such events continuing at the FU-2 visit are to be followed until resolution (as defined above), with evidence of resolution provided on updates to the Drug Safety SAE Form. In the EDC, only documentation of the status of "ongoing" at the FU-2 visit is required.

A summary of the event surveillance (Table H-1) and follow-up requirements (Table H-2) are shown in the following page:

Table H-1: Requirements for Documenting the Incidence of AEs, SAEs, and AESIs:

Event type	Event surveillance period (inclusive):			
	EDC CRF[a]		Drug Safety SAE Form	
	Period start	Period stop	Period start	Period stop
AE: nonserious, non-AESI	first dose	FU-1	NA	NA
SAE: not related	IC	FU-2	IC	FU-2
Related AE leading to study treatment discontinuation	first dose	EOT date	NA (if nonserious)	NA (if nonserious)
AESI: nonserious (AESIs: irAEs, potential DILI, Other; Table 8-1)	IC	FU-2	IC	FU-2
Related SAE	IC	FU-2	IC	ever

AE, adverse event; AESI, adverse event of special interest (Table 8-1); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 days after EOT date; FU-2, follow-up visit 100 days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

Table H-2: Requirements for Following up on Events Documented and Reported in Table H-1:

Event type		Event follow-up requirements			
	If ongoing at…	…follow until…	…and document following on:		
			Source documents	EDC CRF	Drug Safety SAE Form
AE: nonserious, non-AESI	FU-1	NA	status at FU-1	status at FU-1	NA
SAE: not related, non-AESI	FU-2	NA	status at FU-2	status at FU-2	status at FU-2
Related AE leading to study treatment discontinuation	FU-2	Resolution[b]	evidence of resolution	status at FU-2	NA (if nonserious)
AESI: regardless of seriousness (AESIs: irAEs, potential DILI, Other; Table 8-1)	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution
Related SAE	FU-2	Resolution[b]	evidence of resolution	status at FU-2	evidence of resolution

AE, adverse event; AESI, adverse event of special interest (Table 8-1); EDC, electronic CRF data capture system; CRF, case report form; DILI, drug-induced liver injury; EOT date, end of treatment date (later of the date of decision to discontinue study treatment or date of last dose); FU-1, follow-up visit 30 days after EOT date; FU-2, follow-up visit 100 days after EOT date; IC, informed consent; irAE, immune-related AE; NA, not applicable; SAE, serious AE.

[a] See CRF completion guidelines for instructions regarding the appropriate page(s) to be completed

[b] Defined as: AE is fully resolved or ≤ Grade 2 severity or the event is deemed stable/irreversible by the Investigator

Appendix I: EuroQoL Questionnaire EQ-5D-5L, USA (English) Sample Version

Under each heading, please the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

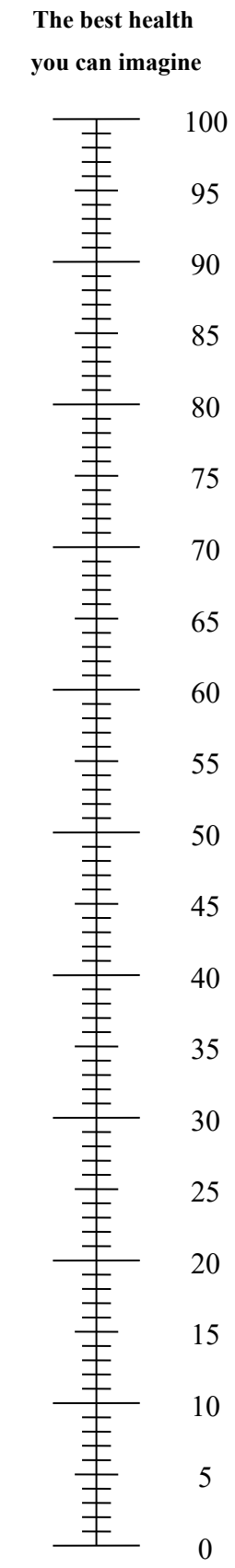
PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is



TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

Appendix J: Child-Pugh Scoring System

Modified Child-Pugh classification of severity of liver disease (Garcia-Tsao et al 2007) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	none	mild/moderate (diuretic-responsive)	tense (diuretic-refractory)
Total bilirubin, mg/dL	≤ 2	2-3	> 3
Albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.7	1.7-2.3	> 2.3
Encephalopathy	none	Grade 1-2 (or precipitant-induced)	Grade 3-4 (chronic)

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

Grade	**Points**	**1-year survival**	**2-year survival**
A: well-compensated disease	5–6	100%	85%
B: significant functional compromise	7–9	80%	60%
C: decompensated disease	10–15	45%	35%

Appendix K: COVID-19 Instructions

This appendix describes contingencies and accommodations to address the COVID-19 pandemic. In response to the evolving circumstances of the pandemic, the Sponsor will provide ongoing guidance to Investigators on study conduct to ensure patient safety and maintain the scientific integrity of the study. Investigators must also maintain awareness of and respond to instructions and guidelines from their local regulatory authorities during the pandemic. These will be temporary measures and are applicable only during the pandemic, and as necessary to abide by local public health requirements. These measures will be repealed back to the measures described in the full study protocol as soon as the situation (governmental rules, benefit/risk assessment for the trial) allows.

Under the exceptional circumstances of the COVID-19 pandemic when randomized subjects may not physically access the site clinic, the accommodations outlined below may be permitted if allowed by local and other applicable regulations (Note: special accommodations are not permitted for screening assessments).

Safety Assessments

Safety assessments should still be performed within the protocol-defined windows with potential modification as outlined below.

If a safety assessment visit cannot take place at the study site, laboratory tests (eg, bloodwork), ECGs, vital signs, and as appropriate, physical exams should be performed remotely (eg, with a local physician), if possible. Any remote laboratory assessments must be performed by laboratories accredited by the local jurisdiction or at the patient's home with a qualified home visit health professional. It is expected that safety laboratory assessments be obtained at every protocol-specified visit and, at a minimum, are to include complete blood count, ALT, AST, total bilirubin, serum creatinine, electrolytes, and (as applicable) pregnancy tests.

In addition, the Investigator or designee must regularly contact the subject (eg, by phone or video call) to ascertain the subject's condition and occurrence of any symptom-based AEs per the relevant protocol-defined visit schedule.

Results of any remote assessments performed by a non-study local oncologist or primary care physician must be sent to the Investigator for review and documentation. If components of the safety assessment cannot be collected or the timing of safety assessments needs to be adjusted, it

may be possible to continue with study treatment, but this must be discussed on a case-by-case basis with the Medical Monitor.

If a safety assessment visit is delayed beyond the protocol-specified window, study treatment must be held until a safety follow-up visit can occur at the study site, at a local health care provider's office, or remotely (eg, via telephone or videoconference). Study treatment can be resumed after a treatment hold if treatment criteria per protocol are met per the Investigator's judgment. Delays in safety assessment visits outside the protocol-defined windows need to be reported as deviations.

Tumor Assessments

Tumor assessments should be continued as required per protocol at the imaging facility where screening scans have been performed or at a qualified local imaging facility. Imaging should be performed within or as close to the study visit window as possible for scheduled imaging time points. If missed or delayed tumor assessments cannot be avoided, study treatment can be continued if safety assessment visits are being conducted and there is no safety concern per Investigator's judgment. Delays in tumor imaging or missed tumor imaging need to be reported as deviations.

Treatment Visits

Administration of study treatment should continue as required per protocol. The study Medical Monitor should be notified if a dose hold is planned beyond the allowed protocol-defined window. Delays in administration of study treatment outside the allowed protocol-defined window need to be reported as deviations.

> *Note: If an interruption of all study treatment for greater than 12 weeks occurs, subjects are required to permanently discontinue study treatment unless permitted to continue by the Sponsor.*

Alternative methods of distribution of oral treatment to subjects may be considered in accordance with the study site's local policies and all applicable regulations. Confirmation of drug receipt will be obtained by sites.

Intravenous study treatment should generally only be administered at the study site, but circumstances may arise where the subject may receive infusions in a satellite site or another study site location but under the supervision of the subject's study site Investigator, with the approval of the Sponsor and in accordance with all applicable regulations.

Informed Consent

Subjects are to be informed of changes to standard procedures resulting from effects of the COVID-19 pandemic, and if necessary subject consent is to be acquired (including consent for remote visits and delivery of oral treatment to subject's home). If additional consent cannot be immediately obtained from the subject in writing, the Investigator is to describe to the subject the additional information requiring consent, obtain verbal consent from the subject, document such consent in the subject file, and follow up with written consent the next time a subject returns to the site. This does not apply to initial consent to enter the study; in this case, written consent is still required.

Subjects Who Develop COVID-19

Subjects who develop COVID-19 while on study may be allowed to continue study treatment if the Investigator determines that the risk-benefit ratio for the subject favors continued treatment, and the Sponsor approves the decision. Any cases of confirmed or suspected COVID-19 infections should follow the general AE reporting requirements defined in the protocol. For any confirmed or suspected COVID-19 cases, the Investigator must assess whether the event should be reported as an SAE using their clinical judgment. The Investigator should further consider whether the diagnosis meets the criteria of being a significant medical event.

Documentation of Data Impacted by COVID-19

If it becomes necessary to employ any of the accommodations described in this appendix of COVID-19 instructions, Investigators are to document each incident in source records as COVID-related. To comply with emerging regulatory guidance that such accommodations be reported and their impact on the study assessed, these will be collected by the Sponsor (or designee) as protocol-deviations. However, no corrective action will generally be expected if this appendix is followed.

When recording data missing, impacted, or related to COVID-19 in the electronic CRFs, the conventions listed in the table below are to be employed. Also refer to updated CRF Completion Guidelines and site communication memos for additional instructions for how to document data missing or impacted by COVID-19.

Case Report Form	Instructions
Adverse Event CRF	• Record COVID-19 diagnoses as "COVID-19". • Record suspected cases as "suspected COVID-19". • If death is the outcome of such an event, the CTCAE grade should be assigned as '5'. Refer to CRF instructions for how to enter fatal events that started at a lower grade.
End of Study Treatment CRFs	• Investigators are to use their best judgment to identify the primary reason for study treatment discontinuation. • If study treatment ended primarily due to a logistical issue associated with the COVID-19 pandemic and was unrelated to cancer progression or any AE: o Indicate "Other" as the reason for treatment discontinuation and describe the reason in the "Specify" field, including the term "COVID-19". o For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions." • If study treatment ended primarily due to an AE caused by COVID-19 or suspected COVID-19: o Indicate "AE/SAE unrelated to progression of disease under study". o Record the AE on the "Adverse Event CRF" as described above with "Action Taken" = "Treatment Discontinued".
End of Radiographic Follow-Up CRF	• If radiographic assessments ended primarily due to a logistical issue or AE caused by COVID-19 or suspected COVID-19: o Indicate "Other" as the reason for discontinuation and describe the reason in the Specify field, including the term "COVID-19." o For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions " or "Subject discontinued due to hospitalization for suspected COVID-19". In the latter example, also record the AE on the Adverse Event CRF as "suspected COVID-19".
Study Treatment CRFs	• If study treatment was held or delayed solely due to a logistical issue associated with the COVID-19 pandemic: o For oral study treatment CRFs: Indicate "Other" as the reason the dosing interval ended and describe the reason in the Specify field, including the term "COVID-19". o For IV dosing CRFs: Enter "Yes" for "Dose delayed from prior infusion". Also, "Reason for dose delay" should be entered as "Other". Describe the reason in the "Specify" field, including the term "COVID-19" (if/when 'Specify' field is available). o For example – Other, Specify: "Subject unable to travel due to COVID-19 restrictions."