Title	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial Comparing CB-839 in Combination with Cabozantinib (CB-Cabo) vs. Placebo with Cabozantinib (Pbo-Cabo) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)
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IND Number	118397
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4.0 CONTACTS

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CORE PROTOCOL

5.0 OBJECTIVES AND ENDPOINTS

Primary Objectives	***Primary Endpoints***
To compare blinded Independent Radiology Committee (IRC)-adjudicated progression free survival (PFS) of patients treated with CB-839 + cabozantinib (CB-Cabo) versus placebo + cabozantinib (Pbo-Cabo) for advanced or metastatic clear-cell RCC (ccRCC)	IRC-adjudicated PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary Objectives	***Secondary Endpoints***
To compare the overall survival (OS) of patients treated with CB-Cabo vs. Pbo-Cabo	Time from randomization to death from any cause
To compare the investigator-assessed PFS of patients treated with CB-Cabo vs. Pbo-Cabo	Investigator-assessed PFS per RECIST v1.1
Additional Objectives	***Additional Endpoints***
To compare the overall response rate (ORR), Duration of Response (DOR), and Disease Control Rate (DCR) of CB-Cabo vs. Pbo-Cabo	Per RECIST v1.1 (see Section 14.6.3)
To compare the safety and tolerability of CB-Cabo vs. Pbo-Cabo	Type, incidence, severity, seriousness, and study drug-relatedness of adverse events
To investigate the pharmacokinetics (PK) of CB-839, cabozantinib, and the major CB-839 metabolite 110826 using sparse PK sampling	Potential relationship between drug and metabolite exposure and the efficacy and safety, as well as evaluate the possible effect of CB-839 on cabozantinib exposure
To investigate the relationship of genetic variants and response to CB-Cabo vs. Pbo-Cabo	Genetic variants and other biomarkers related to angiogenesis, and metabolic pathways
To compare quality of life (QoL) changes from baseline of patients treated with CB-Cabo vs. Pbo-Cabo	Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19) and EuroQol Health questionnaire instrument (EQ-5D-5L)

6.0 SAMPLE SIZE

Approximately 416 evaluable patients are planned for recruitment to this study. Eligible patients will be randomized in a 1:1 ratio (208 patients to the experimental arm and 208 to the control arm).

7.0 STUDY DESIGN

Protocol CX-839-008 is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study comparing two treatment regimens for patients with ccRCC (see Figure 7.0-1). Eligible patients will be randomized in a 1:1 ratio to the following study treatment arms:

a) **CB-Cabo** – CB-839 (800 mg twice daily [BID]) + cabozantinib (60 mg once daily [QD])

b) **Pbo-Cabo** – Placebo + cabozantinib (60 mg QD)

Randomization will be stratified by the following variables:

a) Prior treatment with PD-1/PD-L1 inhibitor therapy (yes vs. no)

b) The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Prognostic Risk Group (favorable vs. intermediate vs. poor; Attachment 3).

The primary endpoint of this Phase 2 study is IRC-adjudicated PFS.

Patients will receive study treatment determined by randomization in 28-day cycles until disease progression per RECIST v.1.1 or unacceptable toxicity, whichever occurs first (see Section 11.3 for further details). Patients will be followed for safety for at least 28 days after the last dose of all study treatments (CB-839/placebo and cabozantinib), or until initiation of a new anticancer therapy, if earlier. Patients who discontinue study treatment for reasons other than disease progression by RECIST v.1.1 or death will also continue to be followed by radiographic tumor imaging until documentation of radiographic progressive disease per RECIST v.1.1, death, initiation of a new anticancer therapy, or withdrawal of consent as described in Section 10.6.9. Long-term follow up for survival will continue until death or withdrawal of consent for survival follow-up.

A summary of the study design is presented in Figure 7.0-1.

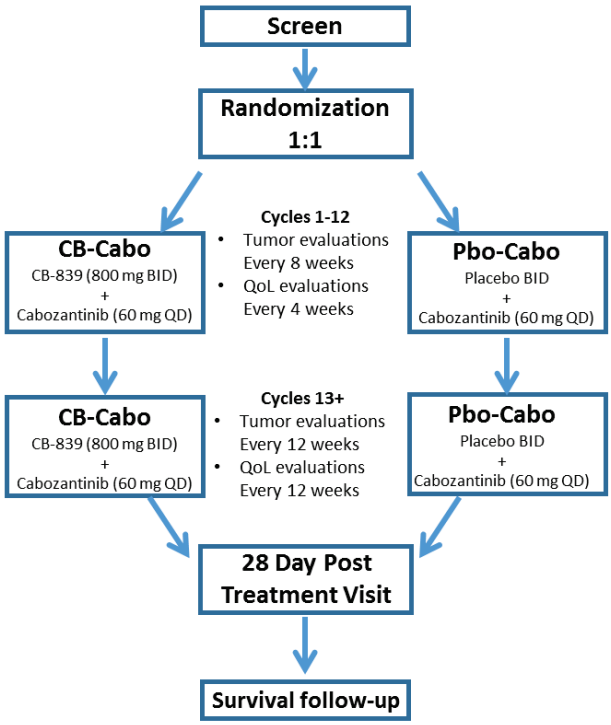

Figure 7.0-1 Study Design Schema

7.1 Study Duration and End of Study Definition

The study will enroll patients over approximately 15 months with approximately 7 months of additional follow-up estimated before reaching the event-driven primary analysis of PFS. The end of study will be defined by the completion of follow-up for the secondary endpoint of overall survival. The projected maximum time required for overall survival follow up is 4 years after the last patient is enrolled. The total duration of the study will be approximately 5 years.

8.0 INCLUSION/ EXCLUSION CRITERIA

8.1 Inclusion Criteria

1. **Informed Consent**
   a. Ability to provide written informed consent in accordance with federal, local, and institutional guidelines
2. **Target Population**
   a. Documented histological or cytological diagnosis of renal cell carcinoma with a clear-cell component
   b. Age ≥ 18 years
   c. Karnofsky Performance Score (KPS) ≥ 70% (Attachment 4)
   d. Estimated Life Expectancy of at least 3 mo
   e. Measurable Disease per RECIST 1.1 as determined by the Investigator (see Attachment 5)
   f. One and not more than two prior systemic lines of therapy (monotherapy or combination regimen) for advanced or metastatic RCC
      1) Must include either:
         i. one anti-angiogenic therapy (any VEGF pathway-targeted agent, used either as monotherapy or as a component of a combination regimen)
         – OR –
         ii. the combination regimen of nivolumab + ipilimumab
      2) Exposure to a prior treatment regimen for ≥4 weeks is considered a prior line of therapy, regardless of reason for its discontinuation (exception: high-dose IL2 will count as prior therapy if >3 doses administered)
         i. 4 weeks will be counted from first to last dose for regimens that are intended to be administered on daily schedules (e.g., sunitinib, pazopanib) and from first dose to end of cycle length after last dose for regimens that are intended to be administered in intervals of ≥ 1 week (e.g., one treatment of a Q2W regimen counts as 2 weeks of therapy)
      3) Rechallenge with the same agent or regimen will not be considered a new line of therapy, if the patient had not previously discontinued that agent or regimen because of disease progression
      4) Systemic adjuvant therapy is considered a prior line of therapy if the patient has disease recurrence on or within 1 year after the last dose of adjuvant therapy
   g. The patient must have had radiographic evidence of disease progression on or after the most recent systemic therapy and within 6 mo before randomization

3. **Laboratory Findings**
   a. Serum creatinine ≤ 2.0 × upper limit of normal or calculated creatinine clearance (C_{Cr}) ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:

C_{Cr} = {((l40 – age) x actual body weight)/ (72 x S_{Cr})} x 0.85 (if female)

b. Adequate hematological function, defined as absolute neutrophil count ≥ 1,500/mm^3, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100,000/mm^3. Transfusions and growth factors must not be used within 2 weeks prior to randomization to meet these requirements.
c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal.
d. Total bilirubin ≤ 1.5 × the upper limit of normal. For patients with Gilbert's disease, ≤ 3 mg/dL (≤ 51.3 µmol/L).
e. Urine protein-to-creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol) or 24-hour urine protein < 1 g.

4. Reproductive Status

a. Female patients of childbearing potential must have a negative serum or urine pregnancy test and if sexually active must agree to contraceptive requirements outlined in Section 10.6.12.2. Male patients who are sexually active with heterosexual partners of childbearing potential must agree to contraceptive requirements and sperm donation restrictions outlined in Section 10.6.12.2.

5. Other Inclusion Criteria

a. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior cancer therapy, unless after discussion with medical monitor adverse events (AEs) are deemed clinically non-significant and/or stable on supportive therapy.

8.2 Exclusion Criteria

1. Medical History

a. Prior treatment with cabozantinib (or other MET inhibitor) or CB-839
b. Receipt of any anticancer therapy within the following windows before randomization:
   - Small molecule receptor tyrosine kinase inhibitor (TKI) therapy (including investigational) within 2 weeks or 5 half-lives, whichever is longer
   - Any type of anticancer antibody or cytotoxic chemotherapy within 4 weeks
   - Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks, or systemic treatment with radionuclides within 6 weeks before randomization. Patients with clinically relevant ongoing complications (per investigator assessment) from prior radiation therapy are not eligible.
   - Other investigational therapy within 4 weeks or 5 half-lives, whichever is longer.

c. Patients with active and/or untreated central nervous system (CNS) cancer are not eligible. Patients with treated brain metastases (1) must have documented radiographic stability of at least 4 weeks duration demonstrated on baseline contrast-enhanced CNS imaging (e.g., contrast-enhanced MRI of the brain) prior to randomization and (2) must be symptomatically stable and off of steroids (for the purpose of treating symptoms of brain metastases) at least 2 weeks before randomization.

d. Any other current or previous malignancy within the past three years except:
   - Adequately treated basal cell or squamous cell skin cancer,
   - Carcinoma in situ of the cervix,
   - Other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Medical Monitor, will not interfere with study-specific endpoints

e. Previously identified allergy or hypersensitivity to components of the study treatment formulations (Note: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take cabozantinib and are also excluded).

f. Corrected QT interval (QTc) > 500 msec within 1 mo before randomization
   - Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with clinically relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

2. Concurrent Conditions

a. Unable to receive oral medications or any condition that may prevent adequate absorption of oral study medication including refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, small bowel resection or gastric bypass surgery, use of feeding tubes

b. Major surgery (e.g., GI surgery) within 6 weeks before first dose of study treatment or incomplete wound healing from any prior surgery. Patients with clinically relevant ongoing complications (per investigator assessment) from prior surgery are not eligible.

c. The patient has uncontrolled, significant current or recent illness including, but not limited to, the following conditions:
   - Cardiovascular disorders:
     i. Symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias
     ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment

- Stroke (including TIA), myocardial infarction, or other ischemic event within 6 mo before randomization
- 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, gastrointestinal perforation, bowel obstruction, or intraabdominal abscess within 6 mo before randomization
    iii. Complete healing of an intra-abdominal abscess must be confirmed before randomization
- Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding within 3 mo before randomization
- Moderate to severe hepatic impairment (Child-Pugh B or C)
- Lesions invading major pulmonary blood vessels

d. Known active infection with HIV or Hepatitis B or C virus
e. Anticoagulation with warfarin at therapeutic doses is prohibited.
    - Note: Anticoagulation with therapeutic doses of low molecular weight heparin (LMWH), direct thrombin inhibitors, factor Xa inhibitors, and platelet inhibitors (e.g., clopidogrel) is allowed in patients without brain metastases who are on stable doses for at least 4 weeks before randomization and have had no complications from the anticoagulation regimen.
    - Low-dose aspirin for cardioprotection, and low-dose (prophylactic) low molecular weight heparin (LMWH) are permitted.
f. Inability to discontinue proton pump inhibitor use before randomization
g. Any condition including social, psychiatric or medical (including uncontrolled significant concurrent illness) that in the opinion of the Investigator could interfere with treatment or protocol-related procedures
h. Patients who are pregnant or lactating

PROTOCOL DETAILS

9.0 BACKGROUND AND RATIONALE

9.1 Renal Cell Cancer

Renal cell carcinoma represents approximately 3% of malignancies, with current worldwide diagnoses and deaths of approximately 295,000 and 134,000 respectively (Hsieh 2017). Approximately a third of patients diagnosed with RCC have curative partial or complete nephrectomy, a third of patients experience disease recurrence following nephrectomy, and a third of patients are diagnosed with *de novo* metastatic disease. Treatment of metastatic RCC (mRCC) is based on disease histology, patient overall health and performance status, and the number and type of prior systemic therapies. First-line patients with clear-cell mRCC typically receive vascular endothelial growth factor (VEGF)-targeted therapy, most commonly the TKIs sunitinib or pazopanib, although the anti-VEGF antibody bevacizumab in combination with low-dose gamma interferon is also an option. After failure of first-line anti-angiogenesis therapy, patients generally receive the anti-PD-1 antibody nivolumab or one of several TKIs (most commonly cabozantinib or axitinib). Patients may receive the mTOR inhibitor everolimus in second line, however this agent is now primarily used in the third-line and later settings.

Despite the availability of multiple approved therapies for the treatment of mRCC in first and second line, these agents represent a limited number of anticancer mechanisms: angiogenesis targeting agents (TKIs or antibodies) or immune modulating agents (PD-1 inhibitor or cytokines). Most importantly, from the standpoint of unmet medical need, very few patients with mRCC are cured by therapy, and a substantial number receive little benefit from treatment. In the second-line setting, based on pivotal studies that lead to marketing approvals in the US and Europe, cabozantinib has an ORR of 17%, median PFS of 7.4 mo and median OS of 21.4 mo (Choueiri 2016), and nivolumab has an ORR of 25%, median PFS of 4.6 mo, and median OS of 25 mo (Motzer 2015). Therefore, there is significant need for improved efficacy in the treatment of mRCC and for the development of therapies with novel and distinct mechanisms of action.

Of importance for the first-line treatment of patients with mRCC, and therefore of importance for the design of second-line clinical studies, data were recently presented at the September 2017 European Society of Medical Oncology Congress in Madrid (Escudier 2017). The Phase 3

randomized CheckMate 214 study compared the combination regimen of nivolumab + ipilimumab to the standard-of-care regimen of sunitinib for the first-line treatment of patients with mRCC. In the primary analysis of patients with intermediate and poor risk disease, the study demonstrated a 37% reduction in risk of death (hazard ratio 0.63, p<0.0001) for the experimental compared to control arm as well as an increased ORR (42% vs. 27%), an increased complete response (CR) rate (9% vs. 1%), and a 3.2-mo improvement in median PFS (p<0.03). In the intent-to-treat (ITT) analysis of all 1096 randomized patients, including favorable-risk patients, the median OS remained significantly improved for the nivolumab + ipilimumab combination compared to sunitinib, with a 32% reduction in risk of death (hazard ratio 0.68, p<0.0003). In addition, the exploratory endpoint of health-related QoL favored the nivolumab + ipilimumab arm over the sunitinib arm. Although these data are not yet reflected in regulatory approval, they are considered to represent a "paradigm shift" in the first-line treatment of mRCC and should be considered in the design of second-line mRCC trials.

In addition, the Phase 2 randomized trial of cabozantinib compared with sunitinib in the first-line treatment of patients with mRCC demonstrated a 52% reduction in the risk of progression or death in patients with intermediate and poor risk disease (adjusted hazard ratio 0.48, p=0.0008; median PFS per IRC 8.6 mo vs. 5.3 mo) and increased ORR (20% vs. 9%) in favor of cabozantinib (Choueiri 2018). These data support the benefit of cabozantinib in patients without prior antiangiogenic therapy and the consideration that second-line mRCC trials including cabozantinib should not be restricted to patients with prior antiangiogenic therapy.

9.2 Glutaminase Inhibitor CB-839

CB-839 is a potent and selective reversible inhibitor of glutaminase activity (Gross 2014). It is an allosteric and noncompetitive inhibitor of glutaminase (GLS gene product), but does not inhibit the liver isoform, glutaminase-2 (GLS2 gene product). (Throughout this document, glutaminase refers to the GLS gene products only.) Incubation of recombinant human glutaminase with CB-839 results in time-dependent and slowly reversible inhibition of glutaminase activity (IC_{50} = 34 nM with 1 hr pre-incubation). Glutaminase inhibition is associated with antiproliferative activity in a wide range of human tumor cell lines *in vitro* and *in vivo* when implanted in immunocompromised mice. The effect of glutaminase inhibition on tumor cell growth closely

correlates with a similar response to withdrawal of glutamine; the absolute requirement of most tumor cells for glutamine involves the production of glutamate by glutaminase.

CB-839 is being developed for the treatment of RCC and other malignancies. Single-agent antitumor activity of CB-839 has been demonstrated *in vitro* in multiple RCC cell lines, and CB-839 has been shown to have antitumor activity in animal studies as a single agent and in combination with drugs such as everolimus, cabozantinib, and sunitinib, where additive or synergistic activity in immunocompromised mice was observed. CB-839 was also shown to enhance the activity of anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors, where there was a significant improvement in the incidence of syngeneic tumor regression in immuno-competent mice. The mechanism of action of CB-839 may involve a combination of a) direct anti-tumor activity resulting from blockade of glutamine utilization and b) indirect stimulation of anti-tumor immune response due to the accumulation of glutamine in the tumor microenvironment.

9.3 Preclinical Activity of CB-839

CB-839 has antiproliferative activity across a wide range of tumor cell types including solid tumors (ccRCC, non-small cell lung cancer, triple negative breast cancer [TNBC], etc.) and hematological tumors (multiple myeloma, acute myeloid leukemia, diffuse large B-cell lymphoma), with IC_{50} values ranging from 1 to 100 nM. When CB-839 was administered twice daily to immunocompromised mice bearing a variety of human tumor xenografts, including ccRCC and TNBC, a reduction of tumor growth rate was observed. CB-839 administration was well-tolerated up to 400 mg/kg BID and resulted in substantial inhibition of tumor growth.

Incubation of cell lines with CB-839 leads to inhibition of glutaminase with a consequent increase in the cellular pools of the substrate glutamine and decrease in the product glutamate and metabolites derived from glutamate. Similar increases in glutamine and decreases in glutamate are observed in xenografted tumors from animals treated with CB-839. In the TNBC cell line HCC1806, inhibition of proliferation and metabolite changes were observed at similar CB-839 concentrations (Gross 2014), consistent with an on-target mechanism of action. Importantly, the antiproliferative activity of CB-839 across cancer cell lines from multiple

histological types (including ccRCC) is associated with inhibition of mTOR signaling, likely resulting from depletion of intracellular pools of nutrient amino acids.

The antiproliferative and pro-apoptotic activity of CB-839 has been characterized in a panel of kidney cancer cell lines (Figure 9.3-1). Clear-cell RCC cell lines appear to be more sensitive to the effects of CB-839 as compared with other kidney cancer cell lines.

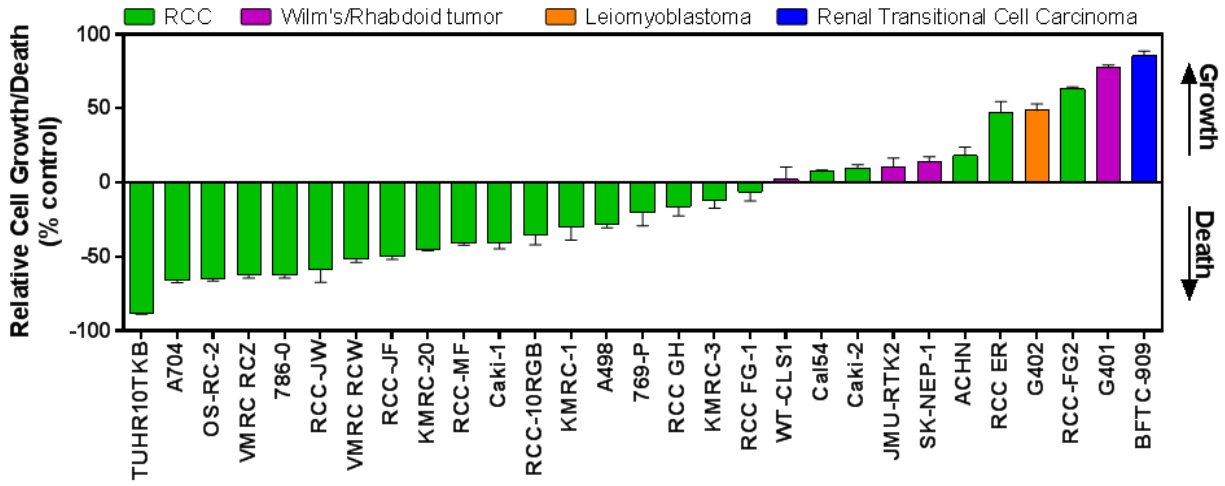

Figure 9.3-1 Antiproliferative and pro-apoptotic activity of CB-839 in kidney tumor cell lines in vitro.
Kidney cancer cells were incubated with 1 µM CB-839 for 72 hr. Cell growth or cell loss (death) relative to vehicle control samples are shown for each cell line on the y-axis.

The combination of CB-839 with the TKI cabozantinib was evaluated *in vitro* and included assessments of a) anti-proliferative activity, b) inhibition of signal transduction via the Ras/Raf pathway, and c) inhibition of oxidative phosphorylation as measured by reduced oxygen consumption. The activity of each drug individually and when given in combination is shown in Figure 9.3-2.

CB-839 has strong synergistic activity in combination with cabozantinib with respect to the inhibition of cellular proliferation (Figure 9.3-2, Panel A). (Note: Combination Index values of 1.0 indicate additivity, and values significantly lower than 1.0 indicate synergy in this assay [Chou 1984]). This may be, in part, due to the enhanced inhibition of VEGF signaling achieved with the combination (Figure 9.3-2, Panel B). Furthermore, there is a greater reduction in aerobic mitochondrial respiration (oxygen consumption) by the combination than either agent alone

(Figure 9.3-2, Panel C), likely due to the dual metabolic inhibition of glucose and glutamine utilization pathways.

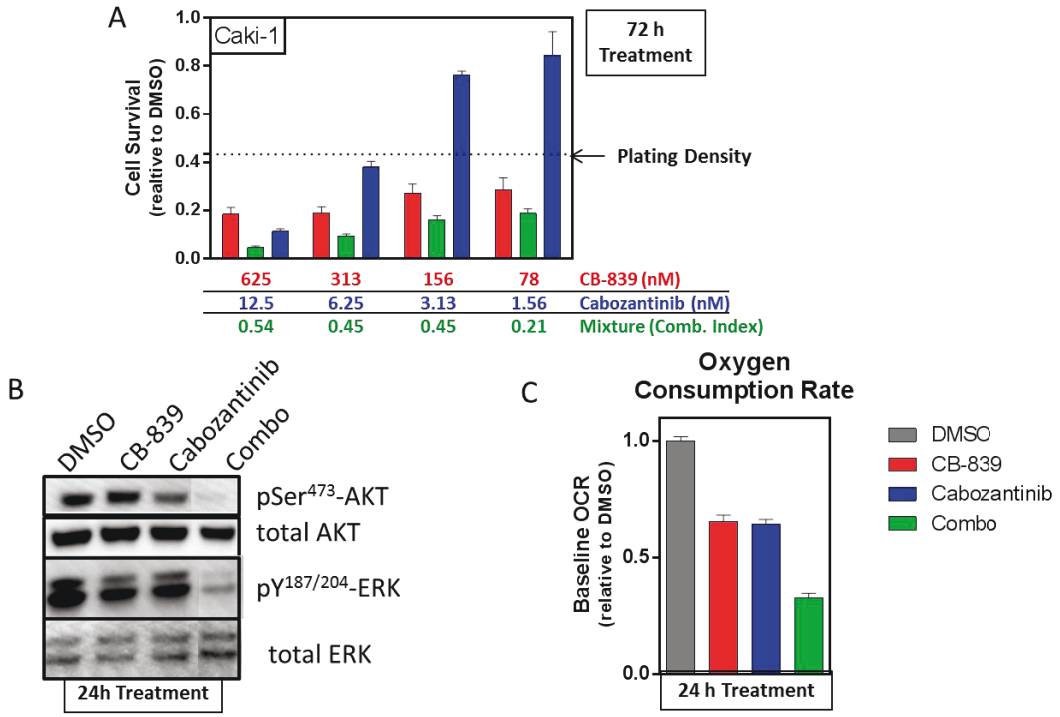

Figure 9.3-2 **Synergistic activity of CB-839 in combination with cabozantinib in the Caki-1 RCC cell line *in vitro*.**
A) Antiproliferative activity in cells treated with a dose range of CB-839 alone, cabozantinib alone, or CB-839 + cabozantinib. Following a 72-hr incubation with compounds, cell viability was measured and normalized to the DMSO-treated control. Representative dose-response profiles and average calculated Chou-Talalay Combination Index values from multiple experiments are shown. B) Inhibition of signaling in the PI3K/mTOR and Ras/Raf pathways is measured by the phosphorylation of AKT and ERK, respectively, in Western blots. C) The inhibition of oxidative phosphorylation is measured by a reduced oxygen consumption rate.

CB-839 potentiates the activity of cabozantinib, as well as other agents that block the Ras/Raf and PI3K/mTOR pathways in ccRCC cell lines (e.g., the mTOR inhibitor everolimus and the TKI sunitinib), in the Caki-1 ccRCC cell line in immunocompromised mice (Figure 9.3-3). Each agent as monotherapy elicited modest tumor growth inhibition, which was substantially increased when dosed in combination. When cabozantinib was administered at a low dose (1 mg/kg QD), synergistic activity was observed (Figure 9.3-3, Panel A). When given at a high dose (10 mg/kg QD), both cabozantinib alone and cabozantinib in combination with CB-839 resulted in complete inhibition of tumor growth. However, when dosing was discontinued in these animals, recovery of tumor growth was more rapid in animals treated with single-agent

cabozantinib than in animals treated with the combination (Figure 9.3-3, Panel B). Importantly, *in vitro* data demonstrate that combination of CB-839 with either everolimus or sunitinib has the same effect on metabolism as was seen in combination with cabozantinib. The translation of these findings to *in vivo* models (Figure 9.3-3, Panels C and D) suggests that the dual metabolic inhibition may be a generalizable combination strategy and further supports the rationale for the combination with everolimus, being tested in the Phase 2 study CX-839-005 as well as cabozantinib, to be tested in this protocol.

Taken together, these data supported the Phase 1 evaluation of CB-839 in combination with cabozantinib and with other inhibitors of the Ras/Raf and PI3K/mTOR pathways.

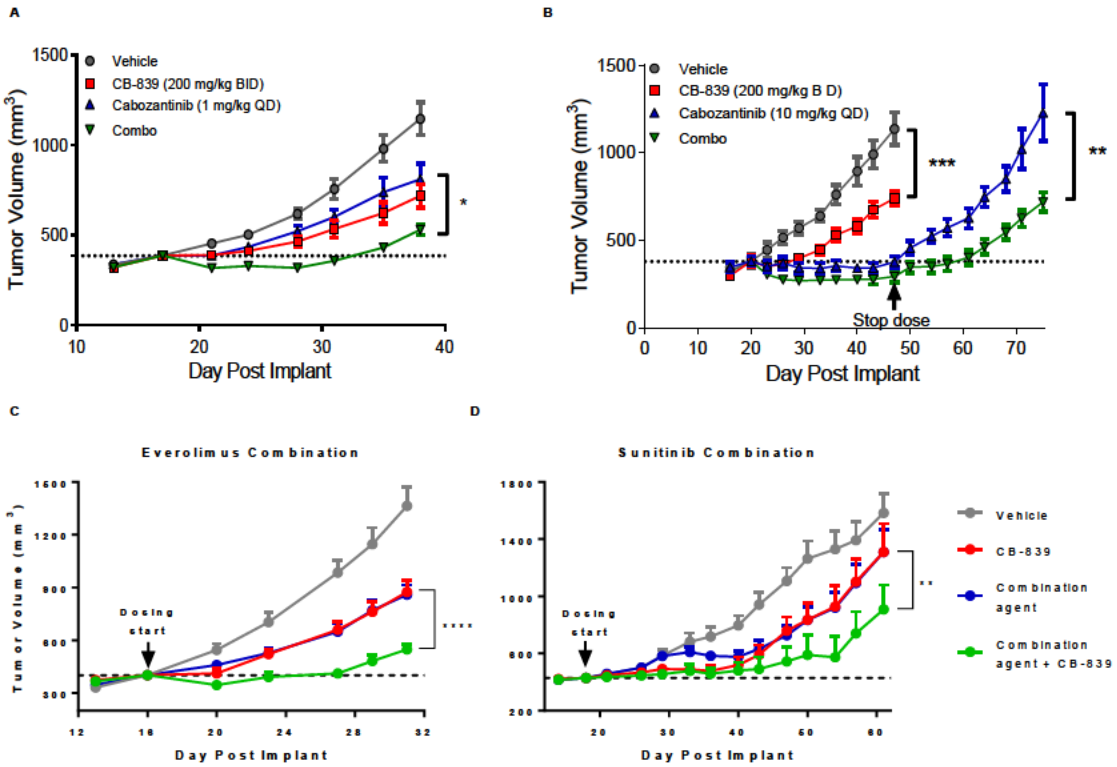

Figure 9.3-3 **Inhibition of tumor growth by CB-839 in combination with other agents in the Caki-1 RCC cell line *in vivo*.**
Tumors were implanted subcutaneously in immunocompromised mice. Animals were randomized to receive vehicle, CB-839 (200 mg BID), combination agent alone, or CB-839 plus combination agent. Cabozantinib was administered in A) a low dose (1 mg/kg QD) or B) a high dose (10 mg/kg) in these studies. C) Everolimus and D) sunitinib were administered on a QD schedule. Tumor growth was measured with calipers and growth rates are expressed in mm^3. Statistical significance for the combination therapy versus either single-agent treatment was calculated for end of study measurements by ANOVA. **p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

9.4 Previous Human Experience with CB-839

Three separate Phase 1 studies were initiated in February 2014 to evaluate the safety, pharmacokinetics, and pharmacodynamics of orally administered CB-839 either as a single agent or in combination with approved agents in patients with solid tumors (CX-839-001), multiple myeloma and Non-Hodgkin's Lymphoma (CX-839-002), or acute leukemia (CX-839-003). CX-839-001 enrolled RCC patients for treatment with CB-839 + cabozantinib and CB-839 + everolimus, as well as TNBC patients for treatment with CB-839 + paclitaxel. In addition, the combination of CB-839 with nivolumab is being evaluated in the Phase 1/2 study, CX-839-004. During dose escalation in all three Phase 1 studies, single-agent CB-839 was administered initially three times daily (TID) without meals and was later changed to a BID schedule with breakfast and dinner.

As of data cuts on 28 September 2017, a total of 102 patients received 600, 800, or 1000 mg BID CB-839 as a single agent; an additional 59 patients received single-agent CB-839 dosed on the TID schedule ranging from 100 to 1000 mg TID. More than 190 patients have received CB-839 at doses ranging from 400 to 800 mg BID in combination with cabozantinib, erlotinib, everolimus, paclitaxel, nivolumab, dexamethasone, pomalidomide, or azacitidine.

In pharmacokinetic studies, the half-life of CB-839 was approximately 4 hr. A dose-related increase in exposure was observed over doses ranging from 100 to 600 mg; exposures for 600 mg and 800 mg doses were similar albeit with significant interpatient variability. In pharmacodynamic studies, robust inhibition of glutaminase was demonstrated in platelets at exposures maintained in most BID-dosed patients at 600 mg and 800 mg inter-dose troughs, with the 800 mg dose in particular showing ≥ 90% target inhibition. Patient tumor biopsies also demonstrated robust glutaminase inhibition (> 75% for most patients).

9.4.1 Safety

Please refer to the current CB-839 Investigator's Brochure for the most recent safety information for CB-839 monotherapy and CB-839 in combination regimens.

CB-839 Monotherapy

Treatment-related AEs for patients enrolled on Study CX-839-001 who received monotherapy with CB-839 on the BID fed regimen are presented in Table 9.5-1. Of 88 safety-evaluable patients, 61 (69.3%) experienced AEs that were considered possibly or probably related to CB-839. The most frequent CB-839-related AEs were fatigue, gastrointestinal AEs (e.g., nausea, decreased appetite, and vomiting), liver function test (LFT) elevations (e.g., AST, ALT), and photophobia. These AEs were typically mild to moderate in intensity (Grade 1/2), reversible, and manageable without dose interruption or modification.

The most frequent Grade 3 AEs were elevations in LFTs, including AST, ALT, and alkaline phosphatase. Gamma-glutamyltransferase elevations were also noted but are of unclear clinical significance. The frequency of Grade 3 elevations in LFTs was limited, with 2 of 88 patients experiencing a treatment-related Grade 3 AST or ALT elevation. One Grade 3 AE of anemia was also considered to be possibly related to CB-839 (not shown). There have been no reported Grade 4 or Grade 5 treatment-related adverse events.

Table 9.5-1: CB-839 Related Adverse Events in ≥ 5% of Patients Treated with Monotherapy CB-839 on the BID Schedule on Study CX-839-001

BID fed - Monotherapy (N=88)		
MedDRA Preferred Term	**Number (%) of patients**	
	All Grades	**Grade 3**
Patients with Any CB-839-Related AE	61 (69.3)	3 (3.4)
Fatigue	22 (25.0)	0
Nausea	20 (22.7)	0
Alanine aminotransferase increased	13 (14.8)	2 (2.3)
Photophobia	12 (13.6)	0
Aspartate aminotransferase increased	10 (11.4)	1 (1.1)
Decreased appetite	7 (8.0)	0
Gamma-glutamyltransferase increased	7 (8.0)	2 (2.3)
Blood alkaline phosphatase increased	6 (6.8)	1 (1.1)

Vomiting	5 (5.7)	0

23July2017 data cut

Photophobia and related ocular toxicities (e.g., photopsia) have been identified as CB-839-related events. In all but one case, these events have been Grade 1 and without impact on patients' daily lives. One photophobia event was characterized as Grade 2. These events appear to occur around C_{max} (1-4 hr after dosing) and resolve over a few hours. These events have been reported to become less frequent over extended dosing. Note: Photophobia/photopsia should be carefully distinguished from "photosensitivity". "Photosensitivity", which refers to an adverse event of the skin such as an unexpected sunburn or dermatitis on sun-exposed skin, has not been observed with CB-839 monotherapy or in combination with cabozantinib.

CB-839 in Combination

CB-839 has been combined in Phase 1 studies with standard of care therapies in a number of different solid tumors, including everolimus (N = 27), cabozantinib (N = 12), paclitaxel (N = 49), nivolumab (N = 82), and erlotinib (N = 1). In all cases thus far, the Adverse Event profile of CB-839 administered at 600-800 mg BID together with the full dose of each partner agent has been similar to those previously reported for each agent alone. Additional details are available in the Investigator's Brochure.

CB-839 + Cabozantinib

Based on the data cut on 23 October 2018 for patients enrolled on the phase 1 Study CX-839-001, treatment-related AEs reported for ≥2 patients among 13 patients receiving CB-839 (6 at 600 mg BID and 7 at 800 mg BID) with cabozantinib 60 mg QD are presented in Table 9.5-2. The combination was well tolerated at the 600 mg BID dose and the 800 mg BID dose of CB-839. The most frequently reported treatment-related AEs (assessed as possibly or probably related to either study drug) were diarrhea, elevations in alanine amino transferase and aspartate amino transferase, decreased appetite, nausea, fatigue, and rash. Grade 3 or Grade 4 events were one event each of Grade 3 diarrhea, Grade 3 hallucination, Grade 3 hypertension, and Grade 4 decreased platelet count, the last of which was the sole dose limiting toxicity (DLT) reported during dose escalation (600 mg BID CB-839 cohort). As with other CB-839 combination

regimens, the recommended Phase 2 dose (RP2D) of CB-839 in combination with full dose cabozantinib was determined to be 800 mg BID. (See Section 11.1.2 for information about cabozantinib monotherapy safety).

Table 9.5-2: CX-839-001 CB-839 + Cabozantinib Treatment-Related Adverse Events[1]

CB-839 600 mg BID or 800 mg BID + Cabozantinib 60 mg (N=13)		
MedDRA Preferred Term	**Number (%) of patients**	
	All Grades	**≥Grade 3[2]**
Patients with any treatment-related AEs[1]	13 (100.0)	5 (38.5)
DIARRHOEA	8 (61.5)	1 (7.7)
ALANINE AMINOTRANSFERASE INCREASED	6 (46.2)	0
DECREASED APPETITE	6 (46.2)	0
ASPARTATE AMINOTRANSFERASE INCREASED	5 (38.5)	0
FATIGUE	5 (38.5)	0
NAUSEA	4 (30.8)	0
RASH	4 (30.8)	0
MUCOSAL INFLAMMATION	3 (23.1)	0
PROTEINURIA	3 (23.1)	0
VOMITING	3 (23.1)	0
WEIGHT DECREASED	3 (23.1)	0
DEHYDRATION	2 (15.4)	0
DYSGEUSIA	2 (15.4)	0
HYPERTENSION	2 (15.4)	1 (7.7)
MUSCLE SPASMS	2 (15.4)	0
PLATELET COUNT DECREASED	2 (15.4)	1 (7.7)
PRURITUS	2 (15.4)	0
STOMATITIS	2 (15.4)	0

[1] Adverse events assessed by investigator as possibly or probably related to either CB-839, cabozantinib or both; preferred terms reported in ≥2 patients.
[2] Additional Grade 3 adverse event of hallucination reported in 1 patient.

CB-839 + Everolimus

As discussed in Section 9.3, the combinations of CB-839 with everolimus and with cabozantinib share a common mechanism of action. Inhibitors of the Ras/Raf and PI3K/mTOR pathways inhibit glucose utilization while CB-839 blocks glutamine utilization. The safety profile of these two combinations together with the preclinical data strongly suggest that this is a tumor-specific mechanism with little impact on normal cells and tissues. The combination of CB-839 with everolimus has been well tolerated to date. Of 27 patients who received CB-839 (400 mg, 600 mg or 800 mg BID with food) in combination with everolimus, the most frequent AEs were anemia, decreased appetite, creatinine increase, fatigue, cough, diarrhea, nausea, and hyperglycemia. Grade 3 treatment-related adverse events were few in number, with the most common being decreased appetite, anemia, fatigue, and mucosal inflammation, and there have been no related Grade 4 events. One event of Grade 3 pruritic rash occurred at the CB-839

400 mg BID dose level and was considered a DLT. The rash was considered related to everolimus and resolved upon a dose reduction of everolimus (CB-839 continued at full dose).

9.4.2 Efficacy of CB-839 plus Cabozantinib

Please refer to the current CB-839 Investigator's Brochure for the most recent efficacy information for CB-839 monotherapy and CB-839 in combination regimens.

As of 24 September 2018, 13 patients have been enrolled and treated on Study CX-839-001, with the combination of cabozantinib and CB-839 (6 pts at 600 mg BID and 7 pts at 800 mg BID). Enrolled patients had received a median of 3 prior lines of therapy (range 0-7, including 1 patient with papillary RCC who had not received prior therapy). Among twelve response-evaluable patients treated with the combination, all have received clinical benefit, including 12 of 12 patients with tumor shrinkage, and among evaluable clear cell RCC patients 5 of 10 (50%) had a partial response (PR) by RECIST 1.1.

A waterfall plot of tumor response is shown in Figure 9.6-4.

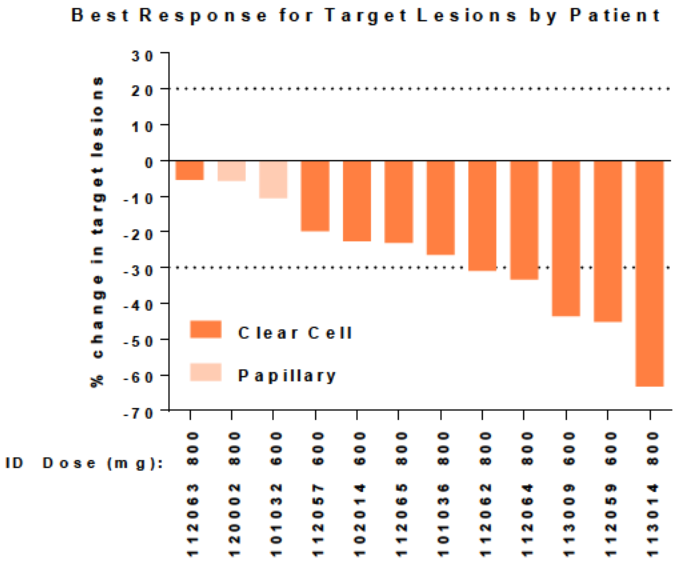

Figure 9.6-4 **Best tumor response for RCC patients receiving CB-839 + cabozantinib in Phase 1.**
Waterfall plot of best change in tumor burden.

9.5 Rationale for CB-839 Dose Selection

CB-839 will be administered at 800 mg BID in combination with full-dose cabozantinib, based on the RP2D determined from the Phase 1 dose escalation study of CB-839 + cabozantinib. One DLT was reported at the 600 mg BID dose level (platelet count decreased); the cohort (N = 6) was completed with no further DLTs. No DLTs were reported in the 800 mg BID CB-839 cohort (N=7). In addition, the 800 mg BID dose of CB-839 has been administered with good tolerability as monotherapy to 22 patients with a variety of solid tumors and to 114 patients in combination therapy with standard of care agents (everolimus, paclitaxel, nivolumab and azacitidine). In pharmacokinetic studies, exposures at the 800 mg BID RP2D and the minus-one dose (600 mg BID) were similar with wide interpatient variability. In pharmacodynamic studies of glutaminase target inhibition in platelets, robust inhibition of glutaminase was demonstrated at CB-839 inter-dose trough levels maintained in most patients at doses of 600 and 800 mg BID. However, all patients treated at the 800 mg BID dose demonstrated ≥ 90% target inhibition in platelets, whereas approximately 20% of patients treated at the 600 mg BID dose level showed target

inhibition < 90%. In aggregate, these data support the risk:benefit ratio of the 800 mg BID CB-839 dose level when given alone or in the presence of a variety of standard of care agents.

10.0 PROCEDURES

This section describes evaluations to be performed during the different periods of this study. All patients must sign an IRB/IEC-approved informed consent prior to starting any protocol-specific procedures, including screening procedures; 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/IEC policies. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent.

10.1 Screening

An IRB/EC-approved Informed Consent Form (ICF) must be signed and dated before any study-specific (i.e., non-standard of care) screening procedures are performed. The ICF must be signed and dated ≤42 days prior to randomization.

To determine a patient's eligibility, patients will undergo required screening evaluations as outlined in Attachment 1. Required screening assessments must be completed within 28 days prior to randomization, unless otherwise indicated. Patients must meet all inclusion criteria and none of the exclusion criteria in order to be deemed eligible and randomized into the study. The investigator is responsible for reviewing all screening data to confirm patient eligibility; a Medical Monitor representing the Sponsor will review a brief eligibility checklist with entries of select screening data to approve patient randomization.

10.1.1 Concomitant Treatment

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drugs.

Non-protocol systemic anticancer treatment, surgical resection of lesions, use of investigational therapeutic agents other than the study drugs, and palliative radiation to non-bone tumors are NOT permitted while the patient is on study. In general, palliative (limited field) radiation for bone metastasis pain should not be performed while on study. If palliative radiation to a bone

lesion is deemed clinically unavoidable for symptoms that in the opinion of the investigator are not due to progressive disease, the investigator must seek Sponsor approval prior to the procedure. Note that these patients may be considered non-evaluable or assigned an early censoring date or progression date at the date of first such therapy. Initiation of therapeutic anticoagulation is allowed on study, as clinically indicated, in consultation with the Sponsor's medical monitor. Chronic use of immunosuppressive medication during study treatment is prohibited with the exceptions of inhaled or topical corticosteroids and corticosteroids with a daily dosage equivalent of ≤ 10 mg prednisone.

CB-839 is metabolized by human hepatocytes primarily through amide hydrolysis. CB-839 does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5µM) *in vitro*. Although CB-839 is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering CB-839 to patients taking drugs that are highly dependent on CYP2C9 for metabolism and have a narrow therapeutic index. A list of medications that are CYP2C9 substrates is provided in Attachment 6.

Preliminary PK data generated in single-agent Phase 1 studies indicate that concomitant use of proton pump inhibitors (PPIs) may reduce absorption of CB-839, resulting in decreased systemic exposure. Discontinuation of PPIs is required for patients on study. Alternative antacids such as H2 blockers (e.g., ranitidine, famotidine) and buffering agents (e.g., sodium bicarbonate, calcium carbonate, and sucralfate) may be substituted for PPIs; however to aid absorption, it is recommended to plan CB-839 dosing at the time of minimal exposure to the antacid (e.g., 10 hr after last dose of H2 blockers, or 2 hr before each dose of H2 blocker if administered BID). Please consult the medical monitor if a patient experiences significant difficulties with gastric symptoms during the study and requires a PPI based on the investigator's assessment.

Cabozantinib is a substrate of CYP3A4, and concomitant use of strong inhibitors or inducers of CYP3A4 may affect cabozantinib exposure. See Attachment 6 for a summary of related data and examples of strong CYP3A4 inhibitors or inducers. Refer to the most current cabozantinib prescribing information for additional details and guidance.

10.1.2 Screening Evaluation

Procedures listed below that are performed as part of the normal standard of care and within the required screening windows (≤ 28 days prior to randomization, unless otherwise specified) may be used for screening purposes:

- Demographic information including date of birth, sex, race, and ethnic origin
- Medical history including review of prior cancer treatments, procedures, and surgeries
- Review of concomitant medications
- Karnofsky performance evaluation
- Complete physical examination including weight and height
- Vital signs
- Standard 12-lead ECG
- Clinical laboratory evaluations; see Attachment 2.
- Serum or urine pregnancy test for females of child-bearing potential
- Radiographic evaluation of tumor burden meeting requirements described in Section 10.6.9
- Brain MRI if history of brain metastases or suggestive symptoms
- Bone scan if history of bone metastases or suggestive symptoms

10.2 Randomization

Patients eligible after completing all screening evaluations will be randomly assigned by an interactive response technology (IRT) system in a 1:1 ratio to receive CB-Cabo or Pbo-Cabo.

Randomization will be stratified by the following factors:

- Prior treatment with PD-1/PD-L1 inhibitor therapy: Yes vs. No
- IMDC Prognostic Risk Group: favorable vs. intermediate vs. poor (Attachment 3)

Randomization should occur as close as possible to the planned start of treatment (i.e., within 24 hr if practicable but no more than 3 days). Patients are defined as enrolled in the study if randomized.

Crossover between treatment arms will not be allowed.

10.3 Study Treatment Procedures

For the complete list of schedules of procedures, please refer to the Schedule of Assessments in Attachment 1.

While the patient is receiving study treatment, the patient's clinical status should be evaluated at each clinic visit to confirm that the patient is suitable for continuing study treatment and to make timely decisions regarding the interruption or restarting of study treatment.

Assessments are based on 28-day cycles. *Radiographic* ***evaluation of tumor burden*** *and* ***QoL questionnaires*** *will be performed as scheduled* ***relative to the date of Cycle 1 Day 1 (C1D1)*** *regardless of study treatment holds or delays.* Additional assessments may occur, as clinically indicated, during unscheduled visits.

After randomization, clinic visits for safety evaluations will occur Day 1 of every cycle (approximately every 4 weeks) for the first 12 cycles. Starting with Cycle 13, safety evaluations will occur every 3 cycles (approximately every 12 weeks). More frequent safety evaluations may be performed if clinically indicated. The final scheduled safety assessment will occur at the End of Treatment Visit. If the study treatment is held due to AEs, Investigators should perform additional safety assessments as clinically indicated.

Radiographic evaluation of tumor burden (e.g., diagnostic computed tomography [CT] scan with intravenous contrast or MRI) will occur during Screening (within 28 days prior to randomization), every 8 weeks after C1D1 for the first 12 cycles, every 12 weeks beginning with Cycle 13, and at the End of Treatment Visit. Radiographic assessments may occur more frequently as clinically indicated.

Quality of life questionnaires will be completed before study drug dosing on C1D1, every 4 weeks after C1D1 for the first 12 cycles, every 12 weeks beginning with Cycle 13, and at the End of Treatment Visit.

Patients who hold or discontinue only one of the study drugs (either CB-839/placebo or cabozantinib) for any reason such as, but not limited to, an AE or surgery, should continue the other study drug on study and continue to have scheduled study visits and procedures per protocol.

10.4 Long Term Follow Up

Patients who are in long-term survival follow-up should be contacted every 3 mo for the first 12 mo following discontinuation of all study treatments (CB-839/placebo and cabozantinib) and every 6 mo thereafter. All reasonable efforts must be made to contact the patient and/or persons authorized by the patient to collect survival status and subsequent anticancer therapy.

10.5 Screen Failures

Patients who sign an informed consent form but are not randomized into the study are defined as screen failures. For all screen failures, the following information will be captured in the electronic data capture (EDC) system: screening number, patient demographics, reason(s) for screen failure, and serious adverse events (SAEs) for study-related procedures through 30 days after the procedure, if applicable.

10.6 Procedure details

This section describes assessments to be performed and recorded in the EDC system.

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory test results.

Please refer to Attachment 1 for the schedule of study assessments. Unscheduled visits and additional assessments may be performed as clinically indicated at any time.

10.6.1 Demographics, Medical, and Cancer History

Demographics at screening will include date of birth (or age if date of birth is not allowed to be collected by local regulations), patient initials, race and ethnicity. Additional information such as medical and cancer history, surgical history, prior radiation history, and prior systemic anticancer treatment history will also be collected.

10.6.2 Physical Examination

Complete physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and the End of Treatment Visit. Symptom-directed physical exams can be done on all other visits. System exams are only required as clinically indicated.

The KPS score (Attachment 4) will be assessed during Screening to determine the patient's eligibility and prognostic risk score according to IMDC criteria (Attachment 3). The KPS will also be used to evaluate the patient's performance at scheduled clinic visits according to Attachment 1.

10.6.3 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position. All patients should be sitting for at least 3 min prior to obtaining vital signs.

10.6.4 Adverse Events

Adverse event information will be collected at study visits and may also be collected via any other forms of communication any time during the study. See Section 15.0 for additional details on recording and reporting AEs and SAEs.

10.6.5 Concomitant Medications

Concomitant medication information will be collected at study visits and may also be collected via any other forms of communication any time during the study. See Section 10.1.1 for details on permitted and protocol-restricted concomitant treatment.

10.6.6 Electrocardiograms

Patients should rest in the supine or semi-recumbent position for at least 5 min before the 12-lead ECG recording is started. ECG recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements.

When performed, the ECG must be reviewed by a qualified physician (or qualified physician's assistant or nurse practitioner), and any clinically important finding should be recorded on the appropriate electronic case report form (eCRF). ECG results will include heart rate, R-R interval, PR interval, QRS interval, QT interval, and QTc interval.

10.6.7 Laboratory Assessments

Laboratory evaluations will be performed as noted in the Schedule of Study Assessments (Attachment 1). The laboratory analytes are listed in Attachment 2. All laboratory assessments will be completed by the site local laboratory and results entered in the EDC system.

Any clinically significant results should be entered as medical history or adverse events in the EDC system.

10.6.8 Patient-Reported Quality of Life Assessment

Quality of life assessments should be completed as scheduled relative to the date of C1D1 regardless of study treatment holds or delay (see Attachment 1).

Patients will be asked to complete two health related QoL assessments. The first is the NCCN-Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19) questionnaire, and the second is the EuroQol Health questionnaire (EQ-5D-5L).

Patients should complete the questionnaires prior to receiving any information on their most recent medical results in order to ensure that their responses will not be influenced by their medical information when completing the questionnaires. If a clinic visit is not possible, patients should complete the questionnaires as per schedule at home and transmit their responses to the site (e.g., mail or email) or return it to the site during the next visit. Upon completion, the site should carefully review for completeness.

10.6.9 Tumor Assessments

Radiographic tumor assessments should be completed as scheduled relative to the date of C1D1 regardless of study treatment holds or delay (see Attachment 1).

Radiographic tumor assessments will include diagnostic quality imaging (CT scan or MRI) of chest/abdomen/pelvis. For patients who have an MRI of the abdomen and pelvis, a CT scan of the chest is also required. An MRI or CT of the brain will also be performed at screening for patients with known or suspected brain metastases and continued post-baseline as clinically indicated. If a CT of the brain is performed, ambiguous results must be confirmed by MRI. For patients with symptoms of spinal compression, MRI of the spine and base of the skull should also be performed. Whole body bone scans will also be performed at screening for patients with known or suspected bone metastases and continued post-baseline as clinically indicated.

The study-specific Imaging Manual should be followed. To ensure image consistency, the same imaging modality and acquisition protocols at the same institution/facility used at screening should be used for subsequent tumor assessments. Ideally contrast-enhanced imaging should be performed at screening and subsequent assessments, including at least post-contrast CT scan of the chest and post-contrast CT or MRI of the abdomen and pelvis. If CT contrast is contraindicated, a non-contrast CT scan of the chest together with contrast-enhanced MRI of the abdomen and pelvis is strongly recommended. If CT or MRI contrast is contraindicated in follow-up tumor assessments after contrast-enhanced imaging at baseline, the same modality without contrast should be performed. All imaging must be acquired and transmitted for central review in original Digital Imaging and Communications in Medicine (DICOM) format per guidelines in the study-specific imaging manual.

For the purpose of patient management and treatment decisions during the course of the study, radiographic response and disease progression will be assessed locally by investigators using RECIST v1.1 (Attachment 5). For the purpose of robust documentation of radiographic progression per IRC:

- If any doubt or ambiguities exist about radiographic progression, Investigators are encouraged to continue study therapy if the patient is tolerating treatment, repeat

radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

- Patients who discontinue study treatment for reasons other than progressive disease by RECIST v1.1 or death will continue to be followed by radiographic tumor imaging until documentation of radiographic progressive disease per RECIST v.1.1, death, initiation of a new anticancer therapy, or withdrawal of consent.

- If study treatment continues beyond Investigator-assessed progression because the patient is receiving clinical benefit from continued treatment (see Section 11.3), radiographic tumor assessments will also continue until the patient discontinues study treatment. This practice has the benefit of providing radiographic studies for IRC review beyond Investigator-assessed progression, which may be helpful in the case of discordance between the Investigator and the IRC regarding the date of progression.

10.6.10 Tumor Biopsies

10.6.10.1 Archival Tumor Biopsies

Archival tumor samples will be provided from all patients unless the archival sample is unavailable. Archival samples should be collected and shipped according to instructions provided in the laboratory manual. Archival tissue blocks or slides freshly cut from those blocks are strongly preferred, due to the concern of tissue stability after exposure. Archival tissue collected from recent time points before enrollment is preferred because it more accurately reflects the current state of the tumor/microenvironment at the time of study entry.

10.6.10.2 Optional Fresh Tumor Biopsies

At North American sites only, optional tumor biopsies, collected as clinically indicated at any point on the study, may be shared with the Sponsor upon patient consent for exploratory biomarker assessment (e.g., predictive/prognostic biomarkers for response). Unless clinically indicated, biopsies should not be obtained from target lesions being followed for disease assessment prior to documentation of disease progression per RECIST v.1.1.

When obtained, tissue from optional tumor biopsies will be used for 1) the analysis of gene expression levels, 2) immunohistochemical/immunofluorescence analysis, and 3) mutation profiling. Tissue may also be used for the evaluation of additional exploratory biomarkers that are not pre-specified in this protocol based upon new scientific literature and/or preclinical data.

10.6.11 Pharmacokinetic Samples

Pharmacokinetic samples will be collected from all patients. Plasma PK samples will be used to measure concentrations of CB-839, 110826 (the major metabolite of CB-839), and cabozantinib, and may be used to measure other associated analytes by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to GLP. Blood samples for PK analysis will be collected at the following time points:

- Cycle 2 Day 1: Pre-dose and 2 hr post dose (± 30 min). Patients must take their morning dose of CB-839 in the clinic.
- Cycle 3, Day 1: 4 hr and 6 hr post dose (± 1 hr). Patients can take their morning dose of CB-839 in the clinic or at home.

The actual time of collection must be noted in the source documents and eCRFs. On Cycle 2 Day 1, patients will have to arrive at the clinic to get their pre-dose PK sample drawn prior to taking their dose in the clinic. Patients must record the times they take their evening dose before Cycle 2 Day 1 and their morning dose on Cycle 3 Day 1 (if they take it at home). In the event that CB-839/placebo dosing is interrupted within 3 days before visits with PK sampling, PK samples should be collected during the next visit that the patient is in the clinic and has taken at least 3 consecutive days of CB-839/placebo. Please consult with the Medical Monitor to determine best options for making up missed PK samples.

Refer to the laboratory manual for details on collection kits and sample processing.

10.6.12 Pregnancy, Contraception and Nursing/Breast-feeding

Patients should be informed that taking the study drugs may involve unknown risks to a fetus (unborn baby) if pregnancy were to occur during study treatment exposure. In order to participate in the study, patients must adhere to pregnancy testing and contraception requirements described below (Clinical Trial Facilitation Group 2014).

10.6.12.1 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal (defined as without menses for >1 year without an alternative medical cause), will have a serum or urine pregnancy test during screening, on C1D1 predose (if screening test >3 days before receiving the first dose of study treatment), and at the End of Treatment Visit. If a urine test is positive or borderline (unable to confirm as negative), a serum β-hCG test will be required. Patients must be excluded in the event of a positive or borderline test result that is not confirmed as negative. Patients who become pregnant on study will be required to discontinue study treatment. Pregnancies occurring during and up to 6 months after completion of study treatment will be reported and followed for outcomes (see Section 15.1).

10.6.12.2 Contraception

Sexually active patients with heterosexual partners must agree that they and their partners will use dual methods of contraception to prevent pregnancy during the course of study treatment and through 4 months after the last dose of all study treatment. Surgically sterilized or postmenopausal female patients (no menses for > 1 year without an alternative medical cause) or male patients with surgically sterilized or postmenopausal female partners are exempt from these requirements. Patients who choose abstinence are exempt from a second method of contraception. Male patients must include a barrier method of contraception (preferably male condom) if sexually active with a female partner of childbearing potential.

Contraception must include at least one highly effective method. Highly effective methods of contraception include:

- combined (estrogen and progestogen containing) hormonal oral, intravaginal or transdermal contraception associated with inhibition of ovulation
- progestogen-only hormonal oral, injectable, or implantable contraception associated with inhibition of ovulation
- intrauterine device
- intrauterine hormone-releasing system
- vasectomised partner
- sexual abstinence

Additional acceptable methods of contraception that are not considered highly effective include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

The following birth control methods are considered unacceptable:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhoea method

Because the absence of pharmacokinetic interactions between hormonal contraception and study treatment cannot be guaranteed, patients should also be counselled that there is potential for hormonal contraception to be less effective. Therefore, if a hormonal contraception is chosen as the highly effective hormonal method, the second method of contraception should be a barrier method (preferably male condom).

Male patients must also agree to refrain from donating sperm during the study and for a minimum of 4 mo following the last dose of all study treatment.

If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

10.6.12.3 Nursing/Breast-feeding

It is not known whether the study drugs and/or their metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue nursing/breast-feeding during treatment with study all study drugs and for at least 4 months after completing therapy.

11.0 POTENTIAL TOXICITIES, DOSE MODIFICATION AND MANAGEMENT OF TOXICITIES

11.1 Potential Toxicities

11.1.1 CB-839

The most frequent AEs considered possibly or probably related to CB-839 monotherapy dosed on the BID schedule on the Phase 1 CX-839-001 study were fatigue, gastrointestinal events (nausea, vomiting, and constipation), photophobia, anemia, dyspnea, and elevations in liver function tests (see Table 9.5-1). These have been primarily Grade 1/2 AEs that have been manageable and reversible with minimal dose modifications or delays.

The most frequent Grade 3/4 AEs considered possibly or probably related to monotherapy CB-839 were LFT elevations (see Table 9.5-1).

11.1.2 Cabozantinib

The safety and tolerability profile of cabozantinib is well defined and outlined in the Cabometyx (cabozantinib) US Prescribing Information (or local equivalent). A summary is provided below:

Adverse events most frequently observed with cabozantinib (≥25% of patients) are diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, hypertension, vomiting, weight decreased, and constipation. The majority of these AEs have been of mild to moderate severity (CTCAE Grade 1-2). Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, hypokalemia, and GGT increased. Cabozantinib has been

associated with a low incidence of severe and potentially lethal AEs, including hemorrhage, GI perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia syndrome, reversible posterior leukoencephalopathy syndrome, and embryo-fetal toxicity (see Warnings and Precautions in the Cabometyx (cabozantinib) US Prescribing Information [or local equivalent]).

11.1.3 Dose Modification Guidelines

11.1.3.1 Study Drug Dose Levels

The possible dose levels for CB-839/placebo and cabozantinib are provided in Table 11.1-1 and Table 11.1-2.

Table 11.1-1: Dose Levels for CB-839/Placebo

Dose Level	CB-839/Placebo Dose
Starting dose	800 mg BID (1600 mg daily)
First dose reduction	600 mg BID (1200 mg daily)
Second dose reduction	400 mg BID (800 mg daily)
Third dose reduction	Discontinue

Table 11.1-2: Dose Levels for Cabozantinib

Dose Level	Cabozantinib Dose
Starting dose	60 mg oral QD
First dose reduction	40 mg oral QD
Second dose reduction	20 mg oral QD
Third dose reduction	Discontinue

11.1.3.2 Study Drug Dose Modifications

Dose modifications may be considered for each study drug independently. Modifications, including dose interruption and resumption, dose reduction, dose re-escalation, and permanent

discontinuation of each study drug will be based on the investigator's discretion, with the following exceptions:

- The dose of each study drug cannot exceed the starting dose
- Interruptions of study drug are allowed for up to 6 weeks (continuous) without Medical Monitor consultation, although it is strongly recommended that interruptions in dosing are as brief as possible. Resumption of study drug in a patient with a dose interruption lasting > 6 weeks requires discussion with and approval by the Medical Monitor (see Section 11.2)
- Both study drugs should be interrupted for Grade ≥ 3 elevated ALT, AST, or bilirubin and restarted at reduced doses after ALT, AST, and bilirubin levels resolve to Grade ≤ 1 or baseline
- Suspected drug-induced liver injury should be reported to the Medical Monitor; both study drugs should be interrupted and then resumed only after discussion with and approval by the Medical Monitor (see Section 11.1.4.2)
- Dose re-escalation is not allowed for a dose reduction triggered by study drug-related myelosuppression or Grade 4 life-threatening AEs affecting major organs
- Permanently discontinue cabozantinib for any of the following:
    - Development of unmanageable fistula or GI perforation
    - Severe hemorrhage
    - Arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
    - Hypertensive crisis or severe hypertension despite optimal medical management
    - Nephrotic syndrome
    - Reversible posterior leukoencephalopathy syndrome

Additional guidelines for treatment modifications and AE management are provided below in Table 11.1-3 and in Section 11.1.4. These guidelines are based on the Cabometyx (cabozantinib) US Prescribing Information and the clinical experience with CB-839, cabozantinib, and the combination to date. Because cabozantinib prescribing information may change over time, the most up-to-date Cabometyx (cabozantinib) US Prescribing Information (or local equivalent) should also be consulted and followed.

These guidelines are intended primarily for toxicities that investigators assess as ***related to study treatment*** (CB-839/placebo or cabozantinib) and that are not easily managed with routine supportive care. In general, all AEs should be managed with supportive care at the earliest signs. Dose interruptions of cabozantinib should be as brief as possible.

Unless otherwise specified (see exceptions under Study Drug Dose Modifications above), dose modifications and AE management guidelines presented in this protocol are only recommendations and are not intended to supersede the clinical judgment of the treating physician.

Table 11.1-3: Treatment Modifications Guidelines for Treatment-Related AEs

Toxicity Grade (CTCAE v4)	CB-839/Placebo	Cabozantinib
Grade 1-2	If manageable and tolerable, continue current dose with supportive care.	
	If not tolerable, interrupt dosing and resume at same dose level upon recovery. If Grade 2 toxicity recurs, interrupt and restart at next lower dose.	
Grade 3 (except non-clinically relevant laboratory abnormalities)	Interrupt dosing and resume at the same dose level or next lower dose level upon recovery.	Interrupt dosing, unless toxicity can be easily managed with a dose reduction, and resume at the next lower dose level upon recovery.
Grade 4 (except non-clinically relevant laboratory abnormalities)	Interrupt dosing immediately. Discontinue study drug unless the patient is deriving clear clinical benefit, as determined by the investigator and agreed by the Medical Monitor, and the toxicity can be managed with a dose reduction and optimal medical care.	

11.1.4 Cabozantinib Warnings, Precautions, and Guidelines for Management of Potential Adverse Events

Below are guidelines for the treatment and/or prevention of certain treatment-emergent AEs of interest that have been associated with, or have a theoretical possibility of occurring with, cabozantinib treatment.

11.1.4.1 Gastrointestinal Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

Diarrhea

Patients should be instructed to notify their study doctor or site staff immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/ antimotility agents is recommended at the first sign of diarrhea as initial management. Some patients may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, consider temporary dose interruption or reduction per Table 11.1-3. When the diarrhea is controlled, retreatment with study treatment may be acceptable per investigator decision.

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

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal 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 nontraumatic cleansing and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

11.1.4.2 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. It is recommended that patients 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 patients who develop increased values of ALT, AST, or bilirubin.

Patients on this study may enter with increased ALT/AST serum levels up to 3 × ULN. Dose reductions of study treatment should be considered in any patient who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A patient who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (see Table 11.1-3) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In patients with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In patients who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and study treatment interrupted. Reinstitution of study treatment after recovery of ALT, AST, and bilirubin to Grade 1 or baseline level must be discussed and approved with the Sponsor.

11.1.4.3 Hematological Disorders

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.

Complete blood counts with differentials and platelets should be performed regularly. Patients with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

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. Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.

11.1.4.4 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure.

Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the investigator's discretion.

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for Grade ≥ 3 anorexia or weight loss. If anorexia and/or weight loss do not recur after a dose reduction, dose of cabozantinib may be re-escalated to the previous dose.

11.1.4.5 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome

Palmar-plantar erythrodysesthesia (PPE) syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated patients. All patients on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30, avoidance of exposure of hands and feet to hot water, protection of pressure-sensitive areas of hands and feet, and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Patients with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual 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. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study treatment are presented in Table 11.1-4.

In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the patient's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Table 11.1-4: Management of Treatment-emergent PPE Syndrome

CTCAE v.4.0 Grade	Action To Be Taken
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. 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.
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 clobetasol 0.05% cream once daily and add analgesics (e.g., NSAIDs/GABA agonists) for pain control if needed. Reassess at least weekly; if PPE does not improve within 2 weeks or worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily and analgesics. Resume cabozantinib at reduced dose if PPE recovers to Grade 1 or 0. Discontinue patient from study if intolerable PPE recurs after dose reduction or does not improve within 6 weeks.

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

Wound Healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the patient is being treated with cabozantinib.

11.1.4.6 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported in patients treated with cabozantinib.

Blood pressure should be monitored in a constant position at each visit (either sitting or supine). Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 11.1-5. In general, patients with known hypertension should be optimally managed prior to study entry. Decisions to decrease or hold the dose of study treatment must be based on blood pressure

readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 11.1-5: Management of Treatment-emergent Hypertension

Criteria for Dose Modification	Action To Be Taken
> 150 to <160 mm Hg (systolic) OR > 100 to <110 mm Hg (diastolic)	• Optimize antihypertensive treatment 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 or < 100 mm Hg diastolic. • If patient is symptomatic interrupt study treatment.
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib treatment by one dose level and add new or additional antihypertensive medications and/or increase dose of existing medications and monitor patient closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. • Interrupt cabozantinib treatment if upper limits of BP (≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic) are sustained and not adequately manageable or if BP is > 180 mm Hg systolic or > 120 mm Hg diastolic or if patient is symptomatic. • Restart cabozantinib treatment at the most tolerable dose and re-escalate cabozantinib dose only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive crisis or hypertensive encephalopathy	• Discontinue cabozantinib treatment

BP, blood pressure.

11.1.4.7 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anti-cancer therapy including inhibitors of VEGF pathways. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal

events. Patients who develop a PE or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (e.g., LMWH) is established. (Note: Initiation of therapeutic anticoagulation is allowed on study in consultation with the Sponsor's medical monitor.) Cabozantinib treatment may be resumed in patients who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment. During anticoagulation treatment, patients need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests according to institutional guidelines. If there are any signs of clinically relevant bleedings, cabozantinib treatment should be interrupted immediately and the sponsor contacted to discuss further study participation. Patients with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and patient is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor.

Arterial thrombotic events (e.g., transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Patients should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac or thromboembolic events that occurred prior to initiation of study treatment. Cabozantinib treatment should be discontinued in patients who develop an acute myocardial infarction or any other clinically relevant arterial thromboembolic complication.

11.1.4.8 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Urine protein should be monitored regularly during cabozantinib treatment. Guidelines for proteinuria management are described in Table 11.1-6. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.

Table 11.1-6: Management of Treatment-emergent Proteinuria

Severity of Proteinuria (UPCR)	Action To Be Taken
≤ 1 mg/mg (≤ 113.1 mg/mmol)	No change in cabozantinib treatment or monitoring
> 1 to < 3.5 mg/mg (> 113.1 to < 395.9 mg/mmol)	• No change in cabozantinib treatment required • Consider confirming with a 24-hour protein assessment within 7 days • Repeat UPCR within 7 days and once per week. If UPCR < 1 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)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1.
Nephrotic syndrome	Discontinue cabozantinib treatment

UPCR, urine protein to creatinine ratio.

11.1.4.9 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Mild hypophosphatemia is usually asymptomatic or symptoms can be non-specific such as weakness, bone pain, rhabdomyolysis, or altered mental status. Other causes of hypophosphatemia such as poor nutrition, chronic alcoholism, malabsorption, excessive antacid use, glucocorticoids use, kidney dysfunction, respiratory alkalosis, vitamin D deficiency should be ruled out and/or these causes treated according to standard of care. Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements according to standard clinical practice guidelines. Clinically relevant hypophosphatemia should be managed according to the dose modification guidelines as outlined in Table 11.1-3 or as clinically indicated.

11.1.4.10 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib and other tyrosine kinase inhibitor treatment as a result of altered thyroid hormone

regulation by mechanisms that seem to be specific for each agent (Torino 2009). Preliminary data from ongoing studies indicate that treatment-emergent elevation of thyroid stimulating hormone (TSH) by cabozantinib may be dose-dependent in fashion. Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Monitor thyroid function as outlined in Attachment 1. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

11.1.4.11 Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, patients should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of patients for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis
- History of clinically significant hemoptysis

Discontinue cabozantinib treatment in patients who have been diagnosed with a severe bleeding complication.

11.1.4.12 GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of

abdominal pain, especially in patients with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI perforation/fistula:

- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or nonsteroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

Complications from radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in patients undergoing treatment with VEGF pathway inhibitors (e.g., bevacizumab). Discontinue cabozantinib treatment in patients who have been diagnosed with GI or non-GI perforation/fistula.

11.1.4.13 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Osteonecrosis has been reported in patients treated with cabozantinib. As a preventive measure, invasive dental procedures should be avoided if possible in patients who have previously been treated with or concomitantly receive bisphosphonates or denosumab.

In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for approximately 4 weeks prior to a dental procedure and resumed after complete healing has occurred.

Patients with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case-by-case basis.

11.2 Resumption of Study Treatment

After withholding a study drug for an adverse event suspected to be related to that study drug, it is generally recommended that administration of the study drug is resumed when the AE has returned to ≤ Grade 1 or baseline; however, investigator discretion may be used to determine if resolution to Grade 1 is necessary prior to reintroducing study treatment. If CB-839/placebo is restarted after permanent discontinuation of cabozantinib, it is also recommended that CB-839/placebo be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in cabozantinib discontinuation. Following a dose reduction of CB-839/placebo or cabozantinib, re-escalation to the previous dose may be allowed at the discretion of the investigator.

11.3 Discontinuation of Treatment

The reasons a patient may discontinue study treatment include, but are not limited to, the following:

- Patient no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date this decision is to be recorded and every effort should be made to continue safety evaluations, tumor assessments, and collection of subsequent anticancer treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment.
- Investigator feels it is not in the best interest of the patient to continue on study.

- Patient participation in another clinical study using an investigational agent or investigational medical device
- Necessity for treatment with other systemic anticancer therapy (non-protocol defined)
- Necessity for withholding study drug for greater than 6 weeks (continuous) for study-treatment related AEs
- Refusal of sexually active fertile patients to use medically accepted highly effective methods of contraception
- Female patient becomes pregnant
- Patient request to discontinue study treatment (with or without concurrent withdrawal of consent)
- Significant patient noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor
- Sponsor request

The Sponsor should be notified of all patient withdrawals (from study treatment or from the study) as soon as possible. The reason for treatment discontinuation, the date of the decision to discontinue treatment, and the date of the last known dose of study treatment will be recorded in the end-of-treatment eCRFs. For patients who withdraw or are withdrawn from study treatment, the investigator should perform all End of Treatment Visit and follow up procedures as indicated in the schedule of study assessments (Attachment 1), and continue protocol-specified evaluations and procedures unless consent to participate in the study is also withdrawn. All patients will be followed until death, unless consent to do so is specifically withdrawn by the patient or until a decision by the Sponsor is made to stop collection of these data. *Note that in order to maximize detection of progression events for the study primary endpoint patients who discontinue study treatment for reasons other than progressive disease or death will continue to be followed by radiographic tumor imaging as described in Section 10.6.9*.

In cases where the investigator believes that a patient is clearly experiencing clinical benefit despite radiographic progression per RECIST 1.1, and that the potential benefit of continuing study treatment outweighs the potential risks, extension of study treatment beyond disease progression may be considered in consultation with the medical monitor. Patients who continue treatment beyond progression will continue to receive all scheduled protocol assessments, including continued radiographic tumor assessments, until study treatment is discontinued.

12.0 TEST ARTICLES/STUDY DRUGS

12.1 Blinded Investigational Product

CB-839 Tablets or Placebo Tablets

Test article (CB-839, 200 mg/tablet) or placebo tablets that are identical in appearance will be administered orally. CB-839/placebo will be administered only to patients who have signed and dated an Informed Consent Form. Tablets should not be cut or crushed and only administered whole. Doses will be administered orally on Days 1 through 28 of each 28-day cycle. Dosing will not be adjusted for body weight or surface area.

The first CB-839/placebo dose of the day will be administered in the morning immediately after breakfast. The evening/second dose should be taken immediately after a meal approximately 12 hr (± 2 hr) after the morning dose. CB-839 ideally should be taken about 2 hr before antacid therapy (see Section 10.1.1).

Guidelines for dose modifications are described in Section 11.1.3.

In the rare event of medical emergency that requires unblinding of treatment assignment, Investigators will have the ability to independently unblind individual patients through the IRT system. Unblinding of the study treatment assignment should be reserved for situations where knowledge of treatment assignment is necessary for critical medical decision-making. Please notify the Sponsor within 1 business day about any unblinding events. Please refer to the pharmacy manual for additional details regarding this process and procedures outlining how to unblind a patient using the IRT system.

12.2 Cabozantinib Study Drug

Cabozantinib Tablets

Cabozantinib (20, 40, or 60 mg/tablets) will be administered only to patients who have signed and dated an Informed Consent Form. Doses will be administered orally on Days 1 through 28 of each 28-day cycle. Patients should not eat for at least 2 hr before and at least 1 hr after taking cabozantinib, and the QD dose of cabozantinib should occur at around the same time every day, preferably at bedtime.

Guidelines for dose modifications are described in Section 11.1.3.

12.3 Missed or Vomited Doses

If a patient does not take a dose of CB-839/placebo within 6 hr after the scheduled time or cabozantinib within 12 hr after the scheduled time, he/she should be instructed to skip that dose and NOT to take extra study drug at their next administration. Patients should be instructed NOT to make up vomited doses of CB-839/placebo or cabozantinib and to report the frequency of vomiting occurrences associated with study drug administration to the site.

12.4 Packaging and Labeling

CB-839 HCl tablets (200 mg) are manufactured, packaged, and labeled according to current GMP. For additional information, please refer to the Pharmacy Manual.

Placebo tablets (200 mg equivalent) are manufactured, packaged, and labeled according to current GMP. For additional information, please refer to the Pharmacy Manual.

Cabozantinib tablets are available as 20-, 40-, or 60-mg strengths. For additional information, please refer to the Pharmacy Manual.

12.5 Storage and Stability

For procedures for the proper handling, storage, preparation and administration of CB-839 tablets or placebo tablets and cabozantinib tablets, please refer to the Pharmacy Manual.

Patients will be requested to store all study treatment at the recommended storage conditions and out of reach and view of children.

12.6 CB-839 Accountability, Reconciliation, and Return

Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

On Day 1 of Cycle 1, patients will be provided with enough study treatment (CB-839/placebo and cabozantinib [ex-US]) to last until their next clinic visit. Patients will return on Day 1 of each cycle thereafter and will receive enough supply until the next visit. The number of CB-839/placebo tablets and cabozantinib tablets remaining from the previous visit will be counted and recorded (as permitted at US sites).

The Investigator or designee must maintain an accurate record of dispensing the study treatment in a drug accountability log, a copy of which must be given to the Sponsor at the end of the study.

Please refer to the Pharmacy Manual for information about return or destruction of study drugs.

12.7 Test Article/Study Drug Compliance

At each clinic visit, patients will be asked to return any unused CB-839 test article/ placebo control article and cabozantinib (ex-US) and will be questioned about their compliance. The number of remaining tablets will be recorded in a drug accountability log. Significant non-compliance (missing > 60% of the study drug for reasons other than documented AE) must be reported to the Medical Monitor.

13.0 Measures to Minimize/Avoid Bias

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient master log.

14.0 STATISTICAL ANALYSIS

This section outlines the statistical analysis strategy and procedures for the study. Additional details of the primary and key secondary analyses will be provided in the Statistical Analysis

Plan (SAP). If, after the study has begun but prior to the final analysis, important changes are made to the protocol that affect principal features of the primary or key secondary analyses, the protocol and/or SAP will be amended, as appropriate.

14.1 General Study Design

This is a multicenter, randomized, double-blind, placebo-controlled Phase 2 study comparing two treatment regimens for patients with advanced or metastatic ccRCC. Patients will be randomized to either CB-839 with cabozantinib or placebo with cabozantinib in a 1:1 ratio. The primary endpoint of this Phase 2 study is IRC-adjudicated PFS. The key secondary endpoint is OS. Patients will be stratified by: a) prior PD-1/PD-L1 inhibitor therapy (yes vs. no) and b) IMDC Prognostic Risk Group (favorable vs. intermediate vs. poor; Attachment 3).

14.2 Independent Radiology Committee (IRC)

An IRC will be established to evaluate tumor scans and relevant history data of trial patients in a central, blinded, and independent fashion. The IRC will comprise board-certified radiologists who will use RECIST 1.1 to assess radiographic disease response and progression following randomization. The IRC will evaluate study data at designated interim (if applicable) and final analyses. Additional details regarding IRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRC Charter.

14.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety and progress 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 patients. IDMC members will be selected for their expertise in oncology. The IDMC will convene periodically and the start date will depend on patient accrual rates. Details of the composition, role, responsibilities, operational considerations, and trial stopping guidelines will be provided in the IDMC Charter.

14.4 Study Steering Committee

A study steering committee will comprise study investigators who are experts in the treatment of RCC who will provide ongoing guidance on issues including protocol design, implementation and interpretation of clinical study results. The steering committee duties and obligations will be outlined in the Study Steering Committee Charter.

14.5 Analysis Patient Sets

14.5.1 Efficacy Analysis Patient Set

The ITT patient set will be the basis for the primary efficacy analysis for this study. The ITT patient set is composed of all randomized patients. Patients in the ITT set will be analyzed for treatment efficacy according to the treatment group to which they are randomized, regardless of post-randomization protocol deviations, including no protocol treatment received.

14.5.2 Safety Analysis Set

All patients who receive any study-specific treatment (CB-839/ placebo or cabozantinib) after randomization will be included in the analysis of safety and analyzed according to the actual treatment received. Patients having taken any CB-839 tablet will be analyzed in the CB-839 with cabozantinib combination arm.

14.6 Efficacy Analysis

14.6.1 Primary Efficacy Endpoint: IRC-Adjudicated PFS

The primary efficacy endpoint is PFS defined as the time from randomization to the earlier of IRC-adjudicated disease progression or death due to any cause. Radiographic disease progression will be assessed using the RECIST v.1.1 criteria. If the disease progression assessment involves more than one date, the earliest date will be used as the event date. The duration of PFS will be censored at the date of the last evaluable radiographic disease assessment prior to the occurrence of any of the following scenarios:

- Patient is alive and progression free at the time of analysis data cutoff

- Disease progression or death occurs after data are missing for two consecutive scheduled radiographic disease assessments, including [a] missing assessments, [b] insufficient data for the assessments, or [c] assessments resulting in a non-evaluable status for overall response per RECIST 1.1.

- Prior to documentation of disease progression or death, patient receives non-protocol anticancer therapy, or any other treatment that in the opinion of the IRC interferes with assessment of disease per RECIST 1.1 (this includes the scenario when the IRC disagrees with the Investigator-judged progressive disease status but the patient received subsequent anticancer therapy).

Patients missing baseline radiographic disease assessment will be censored at the date of randomization (i.e., PFS duration will be 0).

The primary inferential PFS comparison between the two treatment arms will take place when a total of 262 events have been observed. Assuming exponential PFS distributions, patient accrual over a period of 15 months, a median PFS of 8 months for the control arm and a hazard ratio of 0.69 in favor of the experimental arm (equivalent to a 45% increase of median PFS to 11.6 months for the experimental arm), it is estimated that a total of 262 PFS events will occur with 7 months of additional follow-up after accrual completion. The primary analysis will use the stratified log-rank test with the randomization stratification factors of prior PD-1/PD-L1 inhibitor therapy (yes vs. no) and IMDC Prognostic Risk Group (favorable vs. intermediate vs. poor). A 2-sided $p < 0.05$ in favor of the CB-839 + cabozantinib experimental treatment will be regarded as a positive result for the study. The experimental over control hazard ratio will be estimated by a stratified Cox proportional hazards model with the same randomization stratification factors. Kaplan-Meier curves will be presented with median estimates to visually display the progression free survival percentages. In addition, as a secondary analysis for the primary endpoint, the above analyses will be repeated with only two levels, i.e. favorable vs. intermediate/poor, for the IMDC Prognostic Risk grouping.

14.6.2 Secondary Efficacy Endpoints

Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause. For patients alive at the time of analysis, OS will be censored at the time when the patient is last known to be alive. OS analyses will be the similar to the PFS analyses.

14.6.3 Additional Endpoints

Overall Response Rate (ORR)

ORR is defined as the percentage of patients with CR or PR according to the RECIST 1.1 criteria. Response will be adjudicated by the IRC, and response confirmation is not required to compare the two arms in this double-blind protocol. Patients with no evaluable on-study response assessments will be regarded as non-responders. The ORR will be compared between treatment arms by both the Fisher's exact test and a logistic regression analysis accounting for the randomization stratification factors.

Duration of Response (DOR)

For patients achieving a PR or a CR, the duration of response will be calculated as the time between the first documentation of a PR or a CR to the first documentation of PD or death, whichever occurs first. For patients achieving first a PR then a CR, the PR date will be the starting date for response duration calculation. For responders for whom a PD has not been documented yet, Section 14.6.1 conventions regarding PFS censoring will apply. Response duration will be descriptively presented for responders in each treatment arm.

Disease Control Rate (DCR)

DCR is defined as the summed percentage of patients with CR, PR or SD documented at least 8 weeks (-5 day window) following randomization according to RECIST v1.1 criteria.

Patient Reported Outcomes

Patients will be assessed using the NCCN-Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19) questionnaire and the EuroQoL 5D utility score (EQ-5D-5L) and compared between the two treatment arms. Details of the planned analyses for these outcomes will be provided in the SAP.

14.6.4 Exploratory Analyses

To explore the effects of the following baseline factors, a multivariate, stratified Cox model regression analysis will be conducted for PFS. The model will be stratified by the randomization stratification factors and include treatment arm as an independent variable, with the following variables as additional covariates:

- Race (Caucasian vs. all others)
- Sex (male vs. female)
- Age (18–65 vs. > 65 years)
- Number of previous anti-angiogenic therapies (1 vs. >1)

The same analyses will be repeated with only two levels, i.e. favorable vs. intermediate/poor, for the IMDC Prognostic Risk grouping.

Univariate plots will also be presented for descriptive purposes.

14.7 Safety Analysis

Safety will be assessed by the patient incidence and severity of treatment-emergent adverse events (TEAEs). TEAEs are adverse events (AEs) not present prior to protocol treatment, or an already present event that worsens either in intensity or frequency during or following protocol treatment initiation. The analysis will be performed on the Safety Analysis Patient Set as defined in Section 14.5.2.

TEAEs will be coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of patients reporting a given TEAE will be tabulated by treatment group according to the worst severity reported. Separate tables will be constructed for a) all reported TEAEs, b) serious TEAEs, and c) TEAEs leading to permanent discontinuation of study treatment. The above tables will also be presented for TEAEs judged to be related (probably or possibility) to the study treatment.

14.8 Sample Size Estimation

The sample size of 416 patients, randomized 1:1 for CB-839 + cabozantinib vs. placebo + cabozantinib, is anticipated to provide sufficient efficacy data to demonstrate a clinically and statistically significant benefit for CB-839. For the purposes of study design, it is assumed that

the control arm's true median PFS will be approximately 8 months based upon recently published randomized Phase 3 study results with cabozantinib monotherapy (Choueiri 2015), and that the true hazard ratio (HR) favoring CB-839 + cabozantinib over placebo + cabozantinib will be 0.69, corresponding to a clinically significant increase of 45% or 3.6 months from 8 months to 11.6 months.

The proposed study will enroll patients with an accrual period of 15 months and additional follow-up of 7 months. If the control arm's median PFS is 8 months and the true PFS HR of experimental patients to control patients is 0.69, the study will require approximately 208 experimental patients and 208 control patients in order to reject the null hypothesis of equal PFS between the two treatment arms with a power of 0.85. This estimation assumes a 2-sided type I error rate of 0.05, uniform accrual, exponential PFS distributions and the log-rank test for PFS comparison. The expected total PFS event count is 262 under the above assumptions.

15.0 Adverse Events

15.1 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or associated with other protocol interventions in a clinical study. The event does not need to be causally related to the test article. An AE includes, but is not limited to, the following:

- Any AE not previously observed in the patient that emerges during the protocol specified AE reporting period
- Any clinically significant worsening of a preexisting condition
- Complications occurring as a result of protocol-mandated interventions (e.g., invasive procedure such as biopsies), including in the period prior to receiving the first dose of the test article that are related to the protocol-mandated intervention (e.g., medication wash out, biopsies)
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a test article, whether accidental or intentional

- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article
- An AE that has been associated with the discontinuation of the use of a test article

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

A **serious adverse event** (SAE) is an AE that:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clear progression of neoplasia should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular patient)**.** Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. In contrast, all deaths including those related to progression of disease and sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an AE or SAE as appropriate.

Life-threatening, in the context of an SAE, refers to *immediate risk of death* as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, which might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls into the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE. Visits to the Emergency Room that do not result in hospital admission are not considered hospitalizations, but may constitute a medically important event.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Causality Attribution Guidance:

Adverse events should be considered (probably or possibly) treatment-related, unless they fulfill the following criteria (in which circumstances it should be considered unlikely related or unrelated):

- Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or
- The AE has no plausible temporal relationship to administration of the investigational product (e.g., a new cancer diagnosed 2 days after first dose of study drug).

Relatedness to study medication will be graded as either, "probably", "possibly", "unlikely", or "unrelated" as follows:

Probably Related – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly Related – The adverse event

- Follows a reasonable temporal sequence from drug administration

- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Unlikely Related - The adverse event

- Is most likely to be explained by the patient's clinical state or by other modes of therapy administered to the patient

Unrelated – The adverse event

- Does not follow a reasonable sequence from drug administration
- Is readily explained by and considered by the Principal Investigator to be an expected complication of the patient's primary malignancy, clinical state, concurrent medical conditions, or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article, but is considered by the Investigator or the Medical Monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information: certain events, although not considered an SAE, must be recorded, reported, and followed up within the same timelines as for an SAE. These events include:

- A case involving a pregnancy exposure to a test article, unless the product is indicated for use during pregnancy e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, test article must be discontinued immediately. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 6 months after completion of the study treatment must also be reported to the Investigator.

- Overdose and abuse (e.g., a dose higher than that indicated in the protocol) with or without an AE. Overdose and/or abuse are not considered SAEs, but should be reported to the Sponsor expeditiously (within 24 hours of awareness). Overdose and/or abuse should be recorded as an AE in the eCRF and reported to Safety as a non-serious Grade 1 AE using the SAE Report form (by checking the "not applicable" box in the seriousness criterion). If the overdose and/or abuse is/are associated with the following:
    - An AE: both the term overdose or abuse and the associated AE should be recorded in the eCRF as AEs
    - SAE: the term overdose or abuse should continue to be recorded as a non-serious AE in both the eCRF and the SAE report form. In addition, an SAE associated with the overdose/abuse should be reported as an SAE in the SAE Report Form.

15.2 Recording and Reporting

After informed consent, but prior to initiation of study drug, only SAEs caused by protocol-mandated interventions (e.g., a protocol-required blood test) will be collected.

Patients will be followed for AEs or SAEs from the time the patient initiates treatment with the study regimen through at least 28 days after the last dose of all study treatments (CB-839/placebo and cabozantinib), or until initiation of a new anticancer therapy (if earlier). The Investigator must follow up on all drug-related AEs, SAEs, and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer therapy, or in case of permanent impairment, until the condition stabilizes.

All AEs and SAEs must be recorded on source documents and collected in EDC system.

Although AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient, a specific diagnosis should be reported as the AE whenever feasible. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported by the investigator promptly to the Sponsor and IRB/IEC.

15.3 Serious Adverse Event Reporting

All SAEs regardless of attribution, other reportable information, and follow-up information must be reported within 24 hr of learning of the event by completing the SAE form and either emailing or faxing the form to the SAE Reporting Contact. Calithera Biosciences (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Calithera Biosciences will make a determination as to whether the criteria for expedited reporting have been met. The Medical Monitor should also be contacted for any fatal or life-threatening SAE that is considered possibly or probably related to study drug.

Calithera Biosciences, Inc. (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating Investigators, in accordance with FDA regulations *21 CFR 312.32, ICH Guidelines, European Clinical Trials Directive (Directive 2001/20/EC)*, and/or local regulatory requirements and monitoring the safety profile of the study drug. To meet this requirement, Calithera Biosciences, Inc. (or designee) may request additional information from the sites including, but not limited to, hospitalization records. Any requests for such information should be addressed in a timely manner. Additionally, any SAE considered by an Investigator to be possibly or probably related to the study therapy that is brought to the attention of the Investigator at any time outside of the time period specified for SAE reporting also must be reported immediately to one of the individuals listed on the Sponsor contact information page.

Reporting of SAEs by the Investigator to the IRB/IEC will be done in accordance with the standard operation procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

PrimeVigilance, the pharmacovigilance vendor, has been contracted to provide drug safety and pharmacovigilance support, including EudraVigilance management and distribution of SUSAR

reports, in relation to CB-839 investigational medicinal product (IMP) clinical development program by Calithera Biosciences Inc.

16.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The Investigator will also return all CB-839 test articles, containers, and other study materials to the Sponsor or designee, or destroy the materials at the investigative site. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

17.0 INFORMED CONSENT

The Investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The Informed Consent Form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form

18.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval. All protocol amendments must be reviewed and approved following the same process as the original protocol.

19.0 QUALITY CONTROL AND ASSURANCE

The Sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the Investigator review the protocol, the Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

20.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

20.1 Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

20.2 Investigator

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

20.3 Sponsor

The data will be checked for completeness and correctness in real-time online.

Data are checked as they are entered into the EDC system. Off-line checks will also be run to assess the need for additional data review.

20.4 Pre-Study Documentation

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed form 1572 or (for sites outside the US) ICH GCP Statement
- All applicable country-specific regulatory forms
- Current, dated curricula vitae for the Investigator, Sub-Investigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.

- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved Informed Consent Form to be used
- Where applicable, a list of the IRB/IEC members or a Federal-Wide Assurance/ Department of Health and Human Services (FWA/DHHS) number
- Copy of the protocol sign-off page signed by the Investigator
- Copy of the current medical license (online verification is also acceptable) of the Principal Investigator, any Sub-Investigators and any other individuals having significant responsibility as listed in the 1572 (or equivalent)
- Fully executed Clinical Trial Agreement (CTA), if applicable
- Financial disclosure form for the Principal Investigator and any other persons listed in the 1572 (or equivalent)
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the 1572 (or equivalent). The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

20.5 Records Retention

The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (i) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall

have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

21.0 PUBLICATION AND AUTHORSHIP

Results of the study, regardless of outcome, will be submitted for publication in peer-reviewed congresses and/or scientific journals. Per the International Committee of Medical Journal Editors (ICMJE) recommendations, an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1) substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, and 2) drafting the article or revising it critically for important intellectual content, 3) final approval of the version to be published, and 4) agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. All four conditions should be met.

22.0 LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily
C1D1	Cycle 1 Day 1
CB-Cabo	CB-839 plus cabozantinib combination treatment
C_{cr}	Creatinine Clearance
ccRCC	Clear Cell Renal Cell Carcinoma
CFR	Code of Federal Regulations
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease Control Rate
DICOM	Digital Imaging and Communications in Medicine
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLS	Glutaminase
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
IDMC	Independent Data Monitoring Committee

Abbreviation or Term[1]	Definition/Explanation
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Radiology Committee
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
KPS	Karnofsky Performance Score
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LMWH	Low molecular weight heparins
MedDRA	Medical Dictionary for Drug Regulatory Activities
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
ORR	Overall response rate
OS	Overall Survival
Pbo-Cabo	Placebo tablets plus cabozantinib treatment
PD-1	Programmed Cell Death protein 1
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitors
PR	Partial response
PSA	Prostate Specific Antigen
PT	Prothrombin time
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval
RP2D	Recommended Phase 2 Dose
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or Term[1]	Definition/Explanation
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TID	Three times daily
TNBC	Triple negative breast cancer
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VEGF	Vascular Endothelial Growth Factor

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ATTACHMENT 1: SCHEDULE OF STUDY ASSESSMENTS

(1 cycle = 28 days)	Pre-randomization	Post-randomization (Cycle dates are fixed relative to C1D1 and do NOT shift for dose interruptions)			
Visit	**Screening[1]**	**Cycle 1**	**Cycle 2+**	**Cycle 13+ (Every 3 cycles)[2]**	**End of Treatment/ Follow up**
Assessments	≤ 28 days prior to randomization unless otherwise specified	Day 1 (≤3 days post randomization)[3]	Day 1 (± 5 days)	Day 1 (± 7 days)	28 days (+7 days) after treatment discontinuation[4]
Written Informed Consent	X[1]				
Inclusion/Exclusion Criteria	X				
Demographics and Medical History	X				
Physical Examination[5]	X	X[3]	X	X	X
Height	X				
Weight	X	X[3]	X	X	X
Vital Signs[6]	X	X[3]	X	X	X
Karnofsky Performance Status	X	X[3]	X	X	X
12-lead ECG[7]	X		X[7]	X[7]	
Urinalysis[8]	X	X[3,8]	X[8]	X[8]	X[8]
Coagulation Tests[9]	X				
Thyroid Function Tests[10]	X		Every 2 cycles for Cycles 3-13, then as clinically indicated		X
Serum Chemistry	X	X[3]	X	X	X
Hematology	X	X[3]	X	X	X
Serum or Urine Pregnancy Test[11]	X	X[11]			X
PK Sample[12]			X[12]		
CB-839 or Placebo Dosing and Accountability/Compliance		CB-839 or Placebo will be administered twice daily (BID) with food and accountability taken through EOT Visit			
Cabozantinib Dosing and Accountability/Compliance		Cabozantinib will be administered once daily (QD) without food and accountability taken through EOT Visit			
Optional Tumor Biopsy[13]	See Section 10.6.10.2 for details				
Archival Tumor Collection	X				

(1 cycle = 28 days)	Pre-randomization	Post-randomization (Cycle dates are fixed relative to C1D1 and do NOT shift for dose interruptions)			
Visit	**Screening[1]**	**Cycle 1**	**Cycle 2+**	**Cycle 13+ (Every 3 cycles) [2]**	**End of Treatment/ Follow up**
Assessments	≤ 28 days prior to randomization unless otherwise specified	Day 1 (≤3 days post randomization) [3]	Day 1 (± 5 days)	Day 1 (± 7 days)	28 days (+7 days) after treatment discontinuation [4]
Radiographic Evaluation of Tumor Burden	X[14]		Every 8 weeks (± 5 days)[15]	Every 12 weeks (± 7 days)[15]	X[16]
QoL Questionnaires		X	Every 4 weeks (± 5 days)[15]	Every 12 weeks (± 7 days)[15]	X[16]
Adverse Events		Adverse event information will be collected at all study visits and may also be collected via any other forms of communication any time during the study. See Section 15.0 for additional details.			
Concomitant Medications	Concomitant medication information will be collected at all study visits and may also be collected via any other forms of communication any time during the study. See Section 10.1.1 for details				
Survival Follow-up					X[17]

AE = adverse event, CT = computed tomography, ECG = electrocardiogram, MRI = magnetic resonance imaging, QoL = quality of life.

[1] An IRB/EC approved Informed Consent Form (ICF) must be signed and dated ≤42 days prior to randomization. Assessments must be completed within 28 days prior to randomization, unless otherwise indicated. Results of screening assessments must be reviewed before randomization to confirm that the patient meets all eligibility criteria.
[2] Starting with Cycle 13, clinic visits and assessments will be completed at least every 12 weeks. More frequent visits should be completed if clinically indicated.
[3] Assessments on C1D1 should be completed prior to first dose of study treatment; assessments completed during Screening within 3 days of C1D1 are not required to be repeated on C1D1.
[4] Patients will be followed for safety for at least 28 days after the last dose of all study treatments (CB-839/placebo and cabozantinib) or until initiation of a new anticancer therapy, if earlier.
[5] Complete physical exam is required at Screening and at the End of Treatment Visit. A symptom-directed physical exam can be done on all other visits. At Screening patient should be questioned about any symptoms of potential CNS disease (e.g., unusual headaches, falls, changes in balance or coordination, focal weakness, dizziness, seizure, new confusion or memory loss). A positive CNS review of systems should be followed by baseline CNS imaging if not already done.
[6] Patients should be sitting for at least 3 min prior to collection of vital signs (temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure.)
[7] An ECG assessment will be completed at Screening, on Day 1 of Cycles 2-4 and every 3 cycles thereafter.
[8] Post-Screening urinalysis only requires monitoring for proteinuria (dipstick acceptable and if positive will be followed by UPCR).
[9] Coagulation assessment will be completed at Screening and as clinically indicated during the study.
[10] Thyroid function tests include TSH and free-T4 at Screening, then TSH with free-T4 only if TSH is out normal range. Additional testing may be performed as clinically indicated.
[11] Pregnancy testing is required of all females of child-bearing potential. A negative pregnancy test during screening and within 3 days prior to the first dose of study treatment is required. Pregnancy testing on C1D1 is not required if the screening pregnancy test is ≤3 days before the first dose. If a urine test is positive or borderline (unable to confirm as negative), a serum β-hCG test will be required.

[12] PK samples are collected on C2D1: pre-dose and 2 hr post dose, and on C3D1: 4 hr and 6 hr post dose. Refer to the laboratory manual for detailed instructions on samples kits, collection, and shipment to a central laboratory. Contact Sponsor for guidance on options for collecting missed samples.

[13] Optional tumor biopsies to be collected as clinically indicated from patients at North American sites only.

[14] Screening tumor assessments within 28 days prior to randomization accepted. Radiographic assessments should include brain MRI for patients with history of brain metastases or suggestive symptoms and bone scan (bone scintigraphy) for patients with history of bone metastases or suggestive symptoms.

[15] Radiographic tumor assessments and QoL questionnaires will be performed at the scheduled intervals ***relative to the date of C1D1*** regardless of study treatment holds or delays (note that treatment cycles are fixed and do not shift as a result of dose interruptions).

[16] Unless performed within the previous 4 weeks (Note: patients who discontinue study treatment for reasons other than progressive disease [PD] or death will continue to be followed by radiographic tumor imaging until documentation of radiographic PD per RECIST v.1.1, death, initiation of a new anticancer therapy, or withdrawal of consent.)

[17] Patients will be contacted every 3 mo for the first 12 mo afterdiscontinuation of all study treatments (CB-839/placebo and cabozantinib) and every 6 mo thereafter for survival follow-up.

ATTACHMENT 2: CLINICAL LABORATORY TESTS

Hematology (Peripheral Blood Sample):

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count with differential
- Platelet count

Coagulation Tests

- PT, aPTT and INR

Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes

- Phosphate
- Magnesium
- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Glucose
- Blood urea nitrogen[2]
- Total protein
- Albumin
- Total and direct bilirubin[1]
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LDH)
- Creatinine

[1] Direct bilirubin is only required if Total Bilirubin is above the upper limit of normal.

[2] Some sites, particularly in Europe, routinely measure blood urea instead of blood urea nitrogen in the standard of care chemistry panel. Because blood urea nitrogen and blood urea labs serve the same purpose and are interconvertible, either test is acceptable per protocol. The EDC system will allow for either blood urea nitrogen or urea levels to be collected.

Thyroid function tests

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

Pregnancy test (urine or serum β-HCG): Women of child-bearing potential

Urinalysis

Screening:

- Protein
- Leukocyte esterase
- pH

- Glucose
- Ketones
- Hemoglobin
- Nitrite
- Urine protein:creatinine ratio (UPCR) or 24-hour urine protein

Post-Screening:

- Protein (to monitor for proteinuria; dipstick acceptable and if positive will be followed by UPCR)

- Specific gravity
- Urobilinogen

- Microscopic evaluation performed at the discretion of the Investigator based on results of routine urinalysis or as clinically indicated

ATTACHMENT 3: IMDC PROGNOSTIC MODEL

Source: Heng 2009, Heng 2013, Ko 2015

Study patient prognosis will be evaluated using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. The IMDC model was derived from multicenter data from the United States and Canada on 645 patients with no prior antiangiogenic therapy (Heng 2009), and was validated in large studies of patients from multiple international centers in both first-line antiangiogenic targeted therapy and second-line targeted therapy (with or without prior immunotherapy; Heng 2013 and Ko 2015). In the setting of second-line targeted therapy for metastatic RCC, median overall survival was 35 mo in the favorable risk group (0 risk factors), 16.6 mo in the intermediate risk group (1-2 risk factors), and 5.4 mo in the poor risk group (3-6 risk factors; Ko 2015).

Worksheet for Determination of Prognostic Score in Previously Treated Patients
Enter the patient's assessment value in the Patient Value Column. If the patient value meets the criteria then enter "1". To obtain the patient's prognostic score, add up all the "1" entered in last column. The patient's risk group is defined in the table below using the patient's IMDC prognostic score.

Parameter	Risk Factor	Criteria Value	Patient Value	If Patient Value meets criteria, enter 1
Time from diagnosis to initiation of systemic therapy	Shorter time from diagnosis to systemic treatment for metastatic disease	< 1 year		
KPS	Low performance status	< 80%		
Hemoglobin	Low hemoglobin (anemia)	Males: < LLN Females: < LLN		
Corrected calcium	High calcium (hypercalcemia)	> ULN		
Neutrophil	High neutrophil count (neutrophilia)	>ULN		
Platelets	High platelet count (thrombocytosis)	>ULN		
			Sum total **(IMDC Prognostic Score)**:	

KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.
Note: ULN and LLN lab results are according to institution/local lab reference ranges

Use IMDC Prognostic Score to identify patient's risk group in the table below.

Risk Group Based on IMDC Prognostic Score

IMDC Risk Group	IMDC Prognostic Score
Favorable Risk	0
Intermediate Risk	1-2
Poor Risk	3-6

ATTACHMENT 4: KARNOFSKY PERFORMANCE STATUS SCALE

Percent	Description
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of their personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund, fatal processes progressing rapidly.
0	Dead

ATTACHMENT 5: RECIST CRITERIA VERSION 1.1

(Adapted from Eisenhauer 2009)

Sponsor's Notes: CB-839 may affect glucose metabolism in both normal and tumor tissues. Preclinical data suggest that glucose uptake may increase with glutaminase inhibition in sensitive tissues, reflecting the pharmacodynamics effects of CB-839. False positive interpretations of progressive disease with FDG-PET scans may occur. Therefore, all FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI) for this study.

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions will be categorized measurable or non-measurable as follows.

Measurable tumor lesions

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

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. For this protocol, these tumor lesions will be considered non-measurable lesions.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrollment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease (Note: see Section 10.6.9 for protocol-specific requirements; contrast-enhanced MRI of the abdomen and pelvis along with non-contrast CT of the chest is strongly recommended if CT contrast is contraindicated). For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), 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.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion.

Baseline documentation of 'target' and 'non-target' lesions

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

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist

may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

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

Special notes on assessment of progression of non-target disease

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

When the patient also has measurable disease: **In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) For the purposes of this study, progressive disease *should not* be made solely on FDG-PET findings because the mechanism of the study drug, CB-839, may affect glucose metabolism in both normal and tumor tissues. All FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI). The following modifications to RECIST v1.1. will be applied to this study:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. *Confirmation of the new lesion by CT or MRI scan is required per protocol.

- No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new sign of disease confirmed by CT, this is PD
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal *CT scan).
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

*reflects study-specific modification to RECIST v.1.1

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table A: Time Point Response: Patients with Targets (+/- Non-Target) Disease

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

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected

ATTACHMENT 6: DRUG INTERACTIONS

Drug Interactions with CB-839

CYP2C9 Substrates with a narrow therapeutic index	Other CYP2C9 Substrates

• S-Warfarin (anticoagulant)
• Phenytoin (antiepileptic)
	• NSAIDs (analgesic, antipyretic, anti-inflammatory)
	  ○ celecoxib
	  ○ lornoxicam
	  ○ diclofenac
	  ○ ibuprofen
	  ○ naproxen
	  ○ ketoprofen
	  ○ piroxicam
	  ○ meloxicam
	  ○ suprofen
	• fluvastatin (statin)
	• sulfonylureas (antidiabetic)
	  ○ glipizide
	  ○ glibenclamide
	  ○ glimepiride
	  ○ tolbutamide
	  ○ glyburide
	• irbesartanlosartan
	• sildenafil (in erectile dysfunction)
	• terbinafine (antifungal)
	• amitriptyline (tricyclic antidepressant)
	• fluoxetine (SSRI antidepressant)
	• nateglinide (antidiabetic)
	• rosiglitazone (antidiabetic)
	• tamoxifen (SERM)
	• torasemide (loop diuretic) ketamine

*Narrow therapeutic index is defined as "CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)."

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Drug Interactions with Cabozantinib

CYP3A4 Inhibition on Cabozantinib

Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy patients increased single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 38%. Concomitant use of cabozantinib with a strong CYP3A4 inhibitor **increased** the exposure of cabozantinib compared to the use of cabozantinib alone. Reduce the dosage of cabozantinib if concomitant use with strong CYP3A4 inhibitors cannot be avoided.

Examples include: boceprevir, clarithromycin, conivaptan, erythromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, verapamil, and voriconazole

CYP3A4 Induction on Cabozantinib

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy patients decreased single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 77%. Concomitant use of cabozantinib with a strong CYP3A4 inducer **decreased** the exposure of cabozantinib compared to the use of cabozantinib alone. Increase the dosage of cabozantinib if concomitant use with strong CYP3A4 inducers cannot be avoided.

Examples include: rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John's Wort

ATTACHMENT 7: NCCN-FACIT MEASUREMENT SYSTEM (FKSI-19) QUESTIONNAIRE/ SCALE

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4

D
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P

DRS-E	RCC2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

ATTACHMENT 8: EUROQOL QUESTIONNAIRE ED-5D-5L (US ENGLISH SAMPLE VERSION)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

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

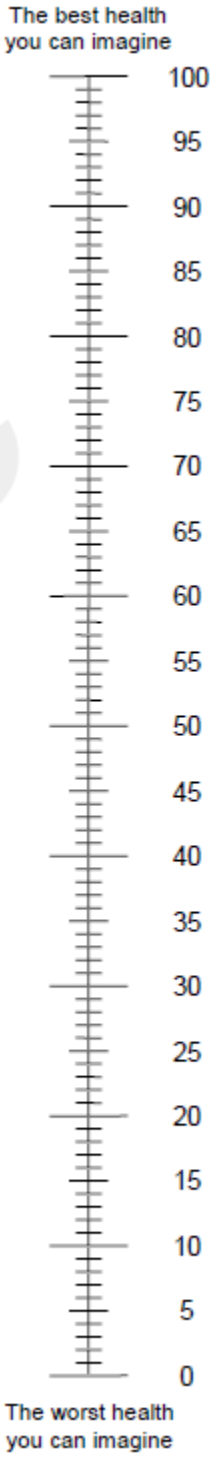
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



ATTACHMENT 9: SUMMARY OF CHANGES (AMENDMENT 3.0 VS. 2.0)

Section	Change	Rationale
4.0	Updated emergency contacts and SAE reporting contact	Result of staff changes
5.0	Additional objectives for PK updated	Included PK analysis of cabozantinib, and the major CB-839 metabolite 110826 using sparse PK sampling. The Population PK analysis will be the subject of a separate report. Clarified that the purpose of the PK analyses are to evaluate the relationship between drug and metabolite exposure and the efficacy and safety, as well as evaluate the possible effect of CB-839 on cabozantinib exposure
8.1	Clarified inclusion criteria 3e	Removed *creatinine* (typo) as described in the protocol clarification letter previously submitted to sites and IRBs/ECs
9.4.1	Added phase 1 study CX-839-001 for the CB-839 + cabozantinib data	Clarified that the CB-839 + cabozantinib data was based on the phase 1 study CX-839-001
9.4.2	Added phase 1 study CX-839-001 for the efficacy of CB-839 plus cabozantinib data	Clarified that the efficacy data of CB-839 + cabozantinib was based on the phase 1 study CX-839-001
10.3	Added instructions for patients who discontinue either CB-839/placebo or cabozantinib	Added language that patients should continue with their scheduled study visits and procedures per protocol if they discontinue either CB-839/placebo or cabozantinib for any reason such as an AE or surgery
10.4	Clarified language for survival follow-up	Clarified that patients will be contacted every 3 months for the first 12 months and every 6 months thereafter after discontinuing CB-839/placebo and cabozantinib for survival follow-up
10.6.11	Included 110826 (major metabolite of CB-839) and cabozantinib for PK analysis	Updated due to revised additional objectives for PK
15.1	Updated other reportable information language	Clarified that other reportable information should be recorded, reported, and followed up within the

		same expedited timelines as for an SAE
15.1	Updated overdose and abuse definition	Added instructions on how to record and report overdoses and abuses depending on whether they are an AE or SAE
15.2	Updated safety follow-up language	Clarified that patients will be followed for AEs or SAEs from initiation of study treatment through at least 28 days after the last dose of all study treatments (CB-839/placebo and cabozantinib) or until initiation of a new anticancer therapy (if earlier)
Attachment 1	Updated window for end of treatment/follow up visit	Included +7 day window per protocol clarification letter previously submitted to sites and IRBs/ECs
Attachment 1	Updated footnote 4	Revised language to match language in section 15.2
Attachment 1	Updated footnote 17	Clarified that patients will be contacted every 3 months for the first 12 months and every 6 months thereafter after discontinuing CB-839/placebo and cabozantinib for survival follow-up
Attachment 2	Added footnote 2 to serum chemistry panel for blood urea nitrogen	Updated per protocol clarification letter previously submitted to sites and IRBs/ECs. Blood BUN and blood urea results will be accepted for blood urea nitrogen tests.

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Reason for signing: Approved	Name: [redacted] Role: B Date of signature: 10-Apr-2020 20:10:23 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: C[redacted]ent Date of signature: 10-Apr-2020 20:52:48 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: R[redacted]irs Date of signature: 11-Apr-2020 00:01:43 GMT+0000

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