Title	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Everolimus (CBE) vs. Placebo with Everolimus (PboE) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)
Protocol Number	CX-839-005
IND Number	118397
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Date/Version	07 August 2018/ Amendment 2

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CORE PROTOCOL

5.0 OBJECTIVES AND ENDPOINTS

Primary Objectives	***Primary Endpoints***
To compare the progression free survival (PFS) of patients treated with CB-839 + everolimus (CBE) versus placebo + everolimus (PboE) for advanced or metastatic clear cell RCC (ccRCC) previously treated with • At least 2 lines of therapy, including at least one vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitor (TKI) • Radiographic progression of mRCC must have occurred (per investigator assessment) on or after the most recent systemic therapy and within 6 mo prior to C1D1.	Investigator-assessed PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary Objectives	***Secondary Endpoints***
To compare the overall survival (OS) of study patients treated with CBE vs. PboE	Assessed by time from randomization to death by any cause
Additional Objectives	***Additional Endpoints***
To compare the objective response rate (ORR), Duration of Response (DOR), and Disease Control Rate (DCR) of CBE vs. PboE	Per RECIST v1.1
To compare the safety and tolerability of CBE vs. PboE	Assessed by type, incidence, severity, seriousness, and study drug-relatedness of adverse events
To investigate the population pharmacokinetics (PK) of CB-839	Analysis of any potential relationship between drug exposure and various population parameters using sparse PK sampling
To investigate the relationship of genetic variants and response to CBE vs. PboE	Genetic variants and other biomarkers related to mTOR, angiogenesis, and metabolic pathways
Change in kidney-cancer related symptoms	Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19)
Change in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health	EuroQol Health questionnaire instrument (EQ-5D-5L)

6.0 SAMPLE SIZE

Approximately 63 evaluable patients are planned for recruitment to this study. Eligible patients will be randomized in a 2:1 ratio to one of the following treatments:

a) **CBE** - The glutaminase inhibitor CB-839 [4 x 200 mg tablets (800 mg) twice daily (BID)] and the mTOR inhibitor everolimus [10 mg once daily (QD)]

b) **PboE** - Placebo tablets [4 tablets BID] and everolimus [10 mg QD]

7.0 STUDY DESIGN

Protocol CX-839-005 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 2:1 ratio to receive CBE vs. PboE. Randomization will be stratified by a) number of prior lines of TKI therapy (1 vs. >1) and b) Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Criteria (Attachment 3) for Previously Treated Metastatic RCC (favorable vs. intermediate/poor risk). The estimated sample size is 63 patients. The primary endpoint of this Phase 2 study is investigator-assessed PFS by RECIST 1.1.

Patients will receive the treatment determined by randomization in 28-day cycles until disease progression or unacceptable toxicity (whichever occurs first). Patients will be followed for 28 additional days from last dose date or early discontinuation of treatment for safety follow-up. Patients who discontinue study treatment for reasons other than disease progression or death will remain in follow-up including protocol-defined imaging. Long-term follow up for survival will continue until death or withdrawal of consent for follow-up.

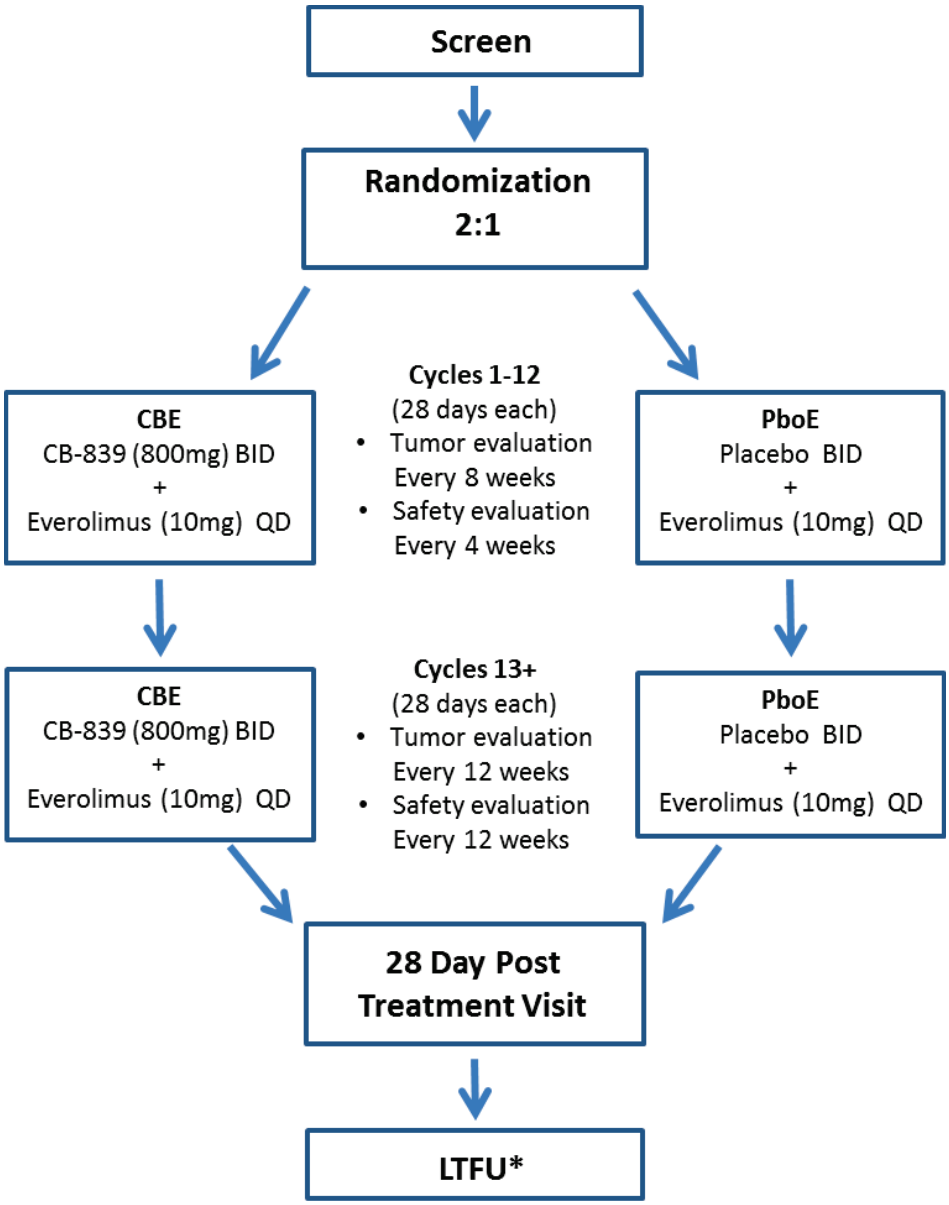

Figure 7.0-1. Study Design Schema: *Long-term follow-up every 3 mo for 1 year from discontinuation of treatment, every 6 mo thereafter

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. Age ≥ 18 years
   b. Karnofsky Performance Score (KPS) ≥ 70% (Attachment 4)
   c. Estimated Life Expectancy of at least 3 mo
   d. Documented histological or cytological diagnosis of renal cell carcinoma with a clear-cell component.
   e. Measurable Disease per RECIST 1.1 as determined by the Investigator (see Attachment 5)
   f. Must have received at least two prior lines of systemic therapy, including at least one VEGFR-targeting TKI (e.g., sunitinib, sorafenib, pazopanib, cabozantinib)
      - Radiographic progression of mRCC must have occurred (per investigator assessment) on or after the most recent systemic therapy and within 6 mo prior to C1D1.
   g. Prior treatment with other anti-cancer therapies including cytokines, monoclonal antibodies, immunotherapies, and cytotoxic chemotherapy is allowed (except for mTOR inhibitors, see Exclusion Criterion #1).
3. **Laboratory Findings**
   a. Serum creatinine ≤ 2.0 × upper limit of normal or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:
   $C_{Cr} = \{((140 - age) \times actual\ body\ weight)/ (72 \times S_{Cr})\} \times 0.85$ (if female)
   b. Adequate hematological function, defined as ANC ≥ 1,500/mm^3, Hb ≥ 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. HbA1c ≤ 8%
   f. Fasting serum triglycerides ≤ 2.5 × upper limit of normal AND total cholesterol ≤ 300 mg/dL (≤ 7.75 mmol/L). Lipid-lowering medication is allowed.
4. **Reproductive Status**
   a. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to the first dose of study drug and agree to use dual

methods of contraception during the study and for a minimum of 3 mo following the last dose of study drug. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. Male patients must use an effective barrier method of contraception during the study and for a minimum of 3 mo following the last dose of study drug if sexually active with a female of childbearing potential. Male patients should not donate sperm for at least 3 months after the last dose of study drug.

5. Other Inclusion Criteria

a. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy.

8.2 Exclusion Criteria

1. Medical History

a. Prior treatment with mTOR inhibitors (everolimus or temsirolimus) or CB-839
b. Receipt of any anticancer therapy within the following windows before randomization:
   - TKI therapy within 2 weeks or 5 half-lives, whichever is longer.
   - Any type of anti-cancer antibody within 4 weeks
   - Cytotoxic chemotherapy within 4 weeks
   - Investigational therapy within 4 weeks or 5 half-lives whichever is longer
   - Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomization. Patients with clinically relevant ongoing complications from prior radiation therapy are not eligible.
c. Any other current or previous malignancy within the past three years except a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, or d) 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

2. Concurrent Conditions

a. Unable to receive medications PO or any condition that may prevent adequate absorption of oral study medication including refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes
b. Major surgery within 28 days prior to randomization

c. Patients with active and/or untreated central nervous system (CNS) cancer are not eligible. Patients with treated brain metastasis must have 1) documented radiographic stability of at least 4 weeks duration demonstrated on baseline contrast-enhanced CNS imaging (eg contrast-enhanced MRI of the brain) prior to randomization and 2) must be symptomatically stable and off steroids for at least 2 weeks before randomization.
d. Unstable/inadequate cardiac function:
    - Symptomatic ischemia or myocardial infarction within the previous 6 mo
    - Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded, 1st degree AV block or asymptomatic LAFB/RBBB are eligible)
    - Congestive heart failure (New York Heart Association class III to IV)
e. Known active infection with HIV or Hepatitis B or C virus
f. Chronic treatment with corticosteroids or other immunosuppressive agents except (i) inhaled or topical steroids or replacement dose corticosteroids equivalent to ≤ 10 mg prednisone and (ii) patients receiving physiological doses of hydrocortisone for adrenal insufficiency
g. Requirement for continued proton pump inhibitor use after randomization
h. 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
i. Patients who are pregnant or lactating

PROTOCOL DETAILS

9.0 BACKGROUND AND RATIONALE

9.1 Renal Cell Cancer (RCC)

The majority of newly diagnosed RCC patients are successfully treated with surgery (partial or complete nephrectomy) alone. One-third of patients develop recurrence after surgery and another 25% present with metastatic disease, in both cases requiring systemic therapy for control of their disease. While there is a growing list of approved agents to treat advanced RCC, including three recent approvals in second line therapy, the broadly applicable agents all fall into one of three mechanistic classes[1]:

- Inhibitors of the vascular endothelial growth factor (VEGF) pathway, comprising small molecule TKIs (sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib) and a monoclonal antibody (bevacizumab)
- Inhibitors of immune checkpoints (a single monoclonal antibody, nivolumab)
- Inhibitors of the mechanistic target of rapamycin (mTOR) pathway (everolimus and temsirolimus)

The current evidence-based treatment continuum employs a TKI in first line therapy, followed in second line by a checkpoint inhibitor or second TKI as monotherapy or lenvatinib paired with everolimus, and in third line by another TKI or nivolumab (depending upon 2nd line choice) or everolimus. The need for effective and tolerable agents in third line and later RCC is driven by improved agents in early therapy and a steady increase in the proportion of patients surviving to receive multiple lines of therapy. For example, a recent review from the International mRCC Database Consortium found that over 20% of patient starting 1st line therapy for metastatic RCC now go on to get 3rd line therapy (Heng 2015). The most common regimens employed in 3rd

[1] High dose interleukin 2 (HD IL-2) falls into a fourth class, cytokine therapy, and is a 1st line therapy with durable benefit but high toxicity in a small proportion of carefully selected patients. Typically HD IL-2 is reserved for a small subset of 1st line patients.

line therapy were everolimus (26%), sorafenib (13%), sunitinib (13%), temsirolimus (11%) and pazopanib (11%). Among 920 pts, the median PFS from the start of 3rd line treatment was 3.4 mo (range 3.2 – 4.4 mo) and median OS 12.4 mo (range 9.9 - 15.5 mo) with overlapping confidence intervals between the various drugs. Everolimus, the most-used drug in 3rd line therapy, had a median PFS of 3.4 mo and median OS of 12.1 mo. The authors concluded from this analysis that third line therapy has demonstrated activity in mRCC, is prevalent in use, and should be offered to clinically eligible patients with mRCC.

Therapy of mRCC in late line (3rd line plus) remains minimally tested in randomized trials and represents an unmet medical need. Many 2nd line drug trials include a small proportion of 3rd line patients, but typically less than 25%. The lack of novel mechanisms, particularly outside of the VEGF TKI realm is also an impediment in the late line setting. It is unclear how many agents with overlapping MOAs and toxicities can be employed in serial fashion before either toxicity or resistance becomes prohibitive.

The mTOR inhibitor everolimus was initially approved for 2nd and 3rd line patients with advanced RCC based upon the results of a pivotal Phase 3 study (Motzer 2010) demonstrating an improvement in median PFS compared to placebo of ~ 2 mo in patients who had previously progressed on either sunitinib or sorafenib or both TKIs (74% of patients being 2nd line and 26% 3rd line). Everolimus has been the dominant agent employed in 2nd line therapy until the past year when it has been surpassed in head-to-head randomized trials in primarily 2nd line patients by the checkpoint inhibitor nivolumab (Motzer 2015a), the TKI cabozantinib (Choueiri 2015), and the combination regimen of the TKI lenvatinib with everolimus (Motzer 2015b); this latter study was entirely 2nd line. As a result of these studies and the resulting new drug approvals, in the US everolimus is now considered primarily in the 3rd line or later setting in mRCC. However, it retains an important place in the treatment continuum due to its distinct mechanism of action compared to the multiple VEGF TKIs and checkpoint inhibitors that are approved in 2nd line or are (in the case of checkpoint inhibitors) being tested in 1st line. Everolimus is generally well tolerated and has a relatively low rate of adverse events, making it an appealing single agent for patients who have already experienced disease progression on 2 or more additional therapies.

The current protocol will evaluate in a randomized, blinded, placebo-controlled setting single agent everolimus as standard of care control arm against the combination of the glutaminase inhibitor CB-839 with everolimus in patients with advanced RCC after prior treatment with at least 2 lines of therapy including at least one TKI. Patients must be demonstrating radiographic progression of mRCC (per investigator assessment) on or after the most recent systemic therapy and within 6 mo prior to C1D1.

9.2 Glutaminase Inhibitor CB-839

CB-839 is an inhibitor of glutaminase 1 that is being developed for the treatment of renal cell cancer and other malignancies. Single agent antitumor activity of CB-839 has been demonstrated *in vitro* in multiple RCC cell lines. 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. Recently, CB-839 was shown to enhance the activity of anti-PD-1 and anti-PD-L1, immune checkpoint inhibitor, 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 immune response due to the accumulation of glutamine in the tumor microenvironment.

CB-839 is a potent and selective reversible inhibitor of glutaminase activity (Gross 2014). It is an allosteric and noncompetitive inhibitor of glutaminase, but does not inhibit the liver isoform, glutaminase-2. 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.

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 (NSCLC), 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 cell lines from multiple histotypes (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.

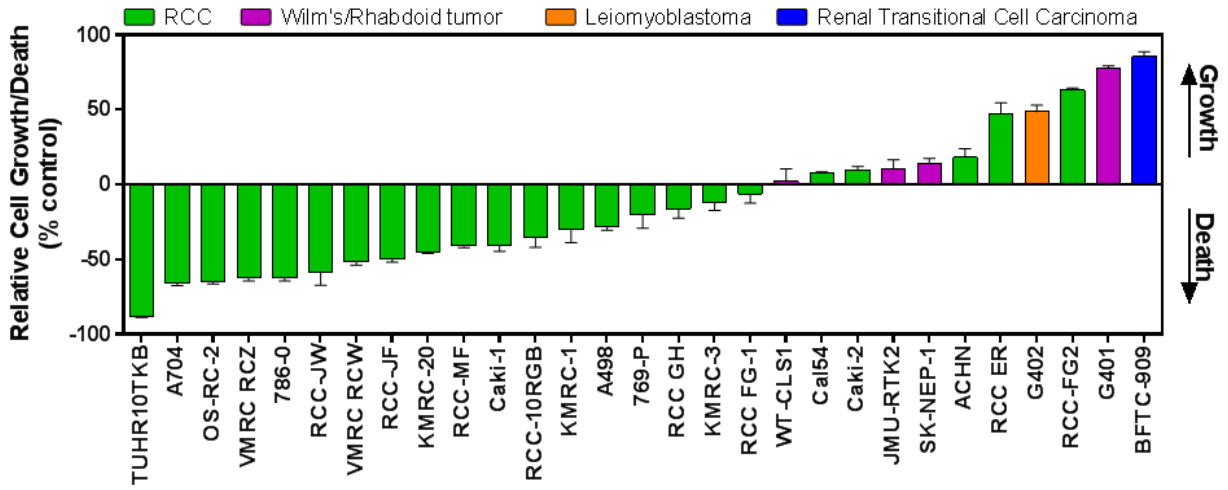

Figure 9.3-1. Antiproliferative and pro-apoptotic activity of CB-839 in kidney tumor cell lines *in vitro*. Kidney cancer cells were incubated with 1 µM CB-839 for 72 hr. Cell growth or cell loss (death) relative to vehicle control samples are shown for each cell line on the y-axis.

CB-839 in combination with the mTOR inhibitor everolimus displays enhanced anti-tumor activity in clear cell RCC models both *in vitro* and *in vivo* in comparison to either agent as monotherapy (Figure 9.3-2). With the ACHN cell line *in vitro*, CB-839 blocks glutamine utilization and everolimus suppresses glucose consumption while the combination inhibits both major nutrient pathways. These metabolic effects with the combination regimen translate into synergistic antiproliferative activity. With the Caki-1 cell line grown as a subcutaneous tumor *in vivo*, the combination of CB-839 and everolimus results in nearly complete arrest of tumor growth whereas each agent individually only partially suppresses tumor growth. These preclinical data provided the rationale for investigating the combination of CB-839 plus everolimus in RCC patients.

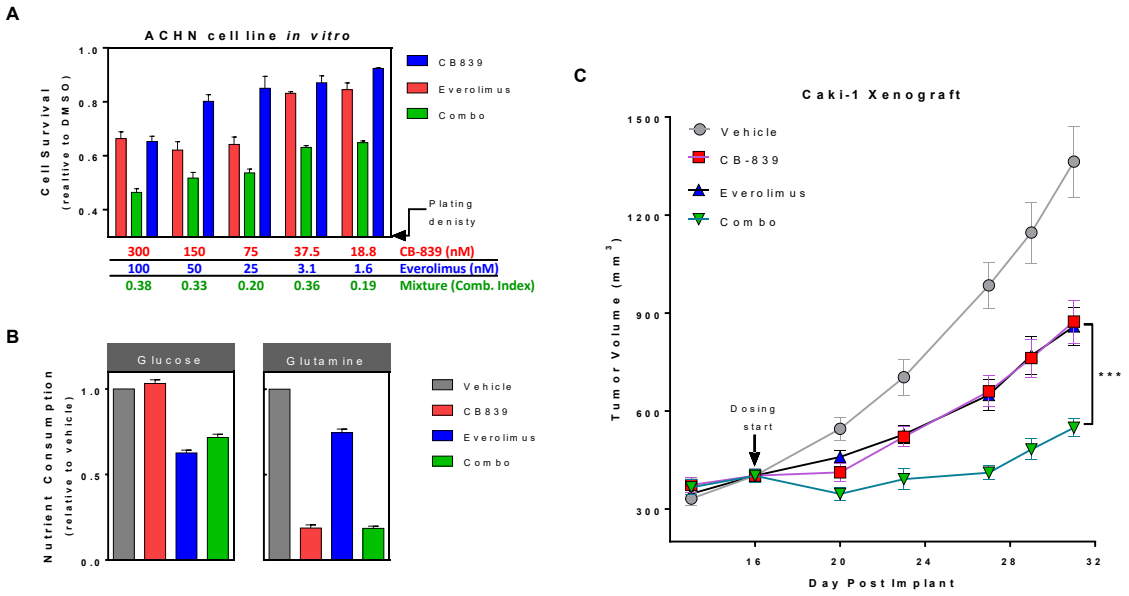

Figure 9.3-2. Synergistic activity of CB-839 in combination with everolimus in clear cell RCC A) Antiproliferative activity in ACHN cells treated with CB-839, everolimus, or CB-839 + everolimus. Following a72 hr incubation, cell viability was normalized to the DMSO-treated control. Representative dose-response profiles and average calculated Chou-Talalay Combination Index (C.I.) values from multiple experiments are shown. B) The consumption of glucose and glutamine from the medium by ACHN cells treated for 24 hr with vehicle, 75 nM CB-839, 25 nM everolimus, or CB-839 + everolimus. C) Inhibition of tumor growth in the Caki-1 RCC cell line *in vivo***.** Tumors were implanted subcutaneously in immunocompromised mice. Animals received CB-839 (200 mg BID), everolimus (1 mg/kg QD), or the two agents in combination. *** $p<0.001$ by ANOVA.

9.4 Previous Human Experience

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 NHL (CX-839-002), or acute leukemia (CX-839-003). CX-839-001 is currently enrolling ccRCC patients for treatment with CB-839 + everolimus and CB-839 + cabozantinib 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 twice daily (BID) with breakfast and dinner. As of data cuts on 23 January 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. A total of 66 patients have received CB-839 at doses ranging from 400 to 800 mg BID in combination with everolimus (19), paclitaxel (31), or azacitidine (16).

In pharmacokinetic studies, the half-life of CB-839 was approximately 4 hr and a dose-related increase in exposure was observed over doses ranging from 100 to 600 mg, with the 600 mg and 800 mg doses being similar due to interpatient variability. In pharmacodynamic studies, robust inhibition of glutaminase was demonstrated in platelets at exposures maintained in most 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).

9.5 Safety

Monotherapy

CB-839 has been well tolerated across all dose levels tested. This section provides a brief summary of the safety and tolerability data for monotherapy CB-839 dosed on the recommended Phase 2 schedule of BID dosing with food in solid tumor patients on study CX-839-001; in total 88 patients received doses between 600 mg and 1000 mg BID for a median of approximately 2 mo. A more complete description of the safety of monotherapy CB-839 is included in the Investigator's Brochure.

The frequency of adverse events in patients receiving monotherapy CB-839 on the BID regimen are provided in Table 9.5-1 (all adverse events) and Table 9.5-2 (CB-839 related adverse events). The large majority of toxicities that have been observed have been Grades 1 and 2 and manageable with supportive care (Table 9.5-1). The primary adverse events that have been observed to date include fatigue, gastrointestinal events (nausea, vomiting, and constipation), photophobia, anemia, dyspnea, and elevations in liver function tests.

The few treatment-related Grade 3/4 toxicities on the BID schedule have included elevations in liver function tests (LFTs), primarily the transaminases ALT and AST (Table 9.5-2). There have

been no treatment-related Grade 4 or Grade 5 adverse events. Although somewhat more frequent on the original TID schedule, Grade 3/4 elevations in LFTs have been relatively infrequent on the BID schedule (3.4% of patients, Table 9.5-1). When they have occurred, these events have been asymptomatic and rapidly reversible upon holding study treatment. In most cases, the patient is able to continue on study following a minus-1 dose reduction of CB-839.

Table 9.5-1: Adverse Events in > 10% of Patients Treated with Monotherapy CB-839 on the BID Schedule on Study CX-839-001

BID Schedule - Monotherapy (N=88): All TEAEs		
MedDRA Preferred Term	**Number (%) of patients**	
	All Events	**≥ Grade 3**
Patients with Any TEAE	83 (94.3)	32 (36.4)
FATIGUE	27 (30.7)	1 (1.1)
NAUSEA	27 (30.7)	1 (1.1)
ALANINE AMINOTRANSFERASE INCREASED	15 (17.0)	3 (3.4)
PHOTOPHOBIA	14 (15.9)	0
CONSTIPATION	13 (14.8)	0
VOMITING	13 (14.8)	2 (2.3)
ANAEMIA	12 (13.6)	5 (5.7)
ASPARTATE AMINOTRANSFERASE INCREASED	12 (13.6)	2 (2.3)
DECREASED APPETITE	12 (13.6)	0
DYSPNOEA	11 (12.5)	2 (2.3)
BLOOD ALKALINE PHOSPHATASE INCREASED	10 (11.4)	2 (2.3)
BLOOD CREATININE INCREASED	10 (11.4)	0
INSOMNIA	9 (10.2)	0

Table 9.5-2: CB-839 Related Adverse Events in ≥ 5% of Patients Treated with Monotherapy CB-839 on the BID Schedule on Study CX-839-001

BID Schedule - Monotherapy (N=88): CB-839 Related TEAEs		
MedDRA Preferred Term	**Number (%) of patients**	
	All Events	**≥ Grade 3^**
Patients with Any CB-839-Related TEAE	61 (69.3)	3 (3.4)
FATIGUE	21 (23.9)	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

^no Grade 4 or Grade 5 events

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 and required the patient rest for 1-2 hr in a dark room. These events appear to occur around C_{max} (1-4 hr after dosing) and resolve with time. Anecdotal reports suggest that these events tend to become less frequent over extended dosing. The AE profile of monotherapy CB-839 using the original schedule (TID without food) as well as the final schedule (BID with food) are described more completely in the Investigator's Brochure.

CB-839 + Everolimus

The combination of CB-839 with everolimus has been well tolerated to date. The frequency of adverse events (reported as of the safety data cut of 23 January 2017) in patients receiving CB-839 on the BID regimen in combination with standard dose everolimus (10 mg QD orally) are provided in Table 9.5-3 (all adverse events) and Table 9.5-4 (treatment related adverse events). Of the first 19 patients who have received escalating doses of CB-839 (7 at 400 mg, 9 at 600 mg and 3 at 800 mg orally BID with food) in combination with everolimus, the most frequent AEs were anemia, decreased appetite, creatinine increase and hyperglycemia; with anemia,

hyperglycemia and fatigue being the most frequent Grade 3/4 AEs. Of note, both patients with G3 hyperglycemia had preexisting diabetes (Table 9.5-3).

Table 9.5-3: Adverse Events in ≥ 3 Patients Treated with CB-839 + Everolimus on Study CX-839-001

CB-839 + Everolimus (N=19): All TEAEs		
MedDRA Preferred Term	**Number (%) of patients**	
	All Events	**≥ Grade 3**
Patients with Any TEAE in CBE Cohort	19 (100.0)	13 (68.4)
ANAEMIA	13 (68.4)	5 (26.3)
DECREASED APPETITE	9 (47.4)	0
BLOOD CREATININE INCREASED	7 (36.8)	0
HYPERGLYCAEMIA	7 (36.8)	2 (10.5)*
COUGH	6 (31.6)	0
NAUSEA	6 (31.6)	0
DIARRHOEA	5 (26.3)	1 (5.3)
HEADACHE	5 (26.3)	1 (5.3)
PROTEINURIA	5 (26.3)	0
VOMITING	5 (26.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	4 (21.1)	0
FATIGUE	4 (21.1)	2 (10.5)
STOMATITIS	4 (21.1)	0
ABDOMINAL PAIN	3 (15.8)	1 (5.3)
ALANINE AMINOTRANSFERASE INCREASED	3 (15.8)	0
CHILLS	3 (15.8)	0
DERMATITIS ACNEIFORM	3 (15.8)	0
DYSGEUSIA	3 (15.8)	0
DYSPNOEA	3 (15.8)	0
HYPOMAGNESAEMIA	3 (15.8)	0
HYPOPHOSPHATAEMIA	3 (15.8)	1 (5.3)
INSOMNIA	3 (15.8)	0
MUCOSAL INFLAMMATION	3 (15.8)	0
MYALGIA	3 (15.8)	1 (5.3)
PAIN	3 (15.8)	1 (5.3)
PLATELET COUNT DECREASED	3 (15.8)	0
PYREXIA	3 (15.8)	0
THROMBOCYTOPENIA	3 (15.8)	0
WEIGHT DECREASED	3 (15.8)	0

*preexisting diabetes

Treatment-related adverse events that were Grade 3 were few in number and there have been no Grade 4 events (Table 9.5-4). One event of Grade 3 rash occurred at the 400 mg BID dose level, which was considered a dose limiting toxicity (DLT). The rash was considered related to everolimus and resolved upon a dose reduction of everolimus (CB-839 continued at full dose). No additional DLTs have been reported in subsequent patients treated at 400, 600 or 800 mg BID and a maximum tolerated dose has not been identified.

Table 9.5-4: Treatment-Related Adverse Events in ≥ 3 Patients Treated with CB-839 + Everolimus on Study CX-839-001

CB-839 + Everolimus (N=19): Treatment-related TEAEs*		
MedDRA Preferred Term	**Number (%) of patients**	
	All Events	**≥ Grade 3^**
Patients with Any Treatment-related TEAE in CBE cohort	19 (100)	9 (47.4)
DECREASED APPETITE	7 (36.8)	0
ANAEMIA	5 (26.3)	1 (5.3)
DIARRHOEA	5 (26.3)	0
HYPERGLYCAEMIA	5 (26.3)	2 (10.5)
PROTEINURIA	5 (26.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	4 (21.1)	0
BLOOD CREATININE INCREASED	4 (21.1)	0
FATIGUE	4 (21.1)	2 (10.5)
NAUSEA	4 (21.1)	0
STOMATITIS	4 (21.1)	0
ALANINE AMINOTRANSFERASE INCREASED	3 (15.8)	0
DERMATITIS ACNEIFORM	3 (15.8)	0
DYSGEUSIA	3 (15.8)	0
MUCOSAL INFLAMMATION	3 (15.8)	0
MYALGIA	3 (15.8)	0
THROMBOCYTOPENIA	3 (15.8)	0
VOMITING	3 (15.8)	0

^no Grade 4 or Grade 5 events
*considered to be at least possibly related to either CB-839 or everolimus

Please refer to the most recent CB-839 Investigator's Brochure for additional safety information from the Phase 1 studies.

9.6 Efficacy of CB-839 + Everolimus

As of the efficacy data cut of 25 October 2016, the CB-839 plus everolimus portion of Phase 1 clinical trial CX-839-001 had enrolled patients with ccRCC (N=14), papillary RCC (N=3), chromophobe RCC (N=1) and FH-mutant RCC (N=1). The CX-839-005 study will enroll only ccRCC patients; therefore this efficacy summary will focus on only the ccRCC patients. For the 14 ccRCC patients that have received the combination of CB-839 and everolimus, all patients had received 2 or more prior lines of therapy with 6 (43%) having received at least 3 prior lines of therapy. Prior therapies included mTOR inhibitors (2 patients), PD-1 inhibitors (9 patients), and at least one TKI (all patients), and 29% of patients had received at least 2 prior TKIs.

Of the 14 ccRCC patients enrolled, 12 were evaluable for efficacy as of the data cut (one patient discontinued prior to the first tumor assessment and one patient was on study prior to first scan). Among the 12 evaluable ccRCC patients, one achieved a partial response (PR) and no patient had disease progression at their first scan at 8 weeks, resulting in a disease control rate (DCR = CR + PR + SD) of 100% (Table 9.6-1). Seven of eight patients that had reached the second scan timepoint at 16 weeks continued to show disease control (an additional four patients remained on study between the first and second scans). Although small numbers, these data are notable for the low rate of progression in patients at the first two time points, since monotherapy everolimus in 2nd line RCC has shown 30-40% progressive disease (PD) at the first scan (8 weeks) and approximately 50% PD at the second scan (16 weeks).

Table 9.6-1: Efficacy of the CB-839 + Everolimus Combination

	Clear cell RCC
Response Evaluable (N)	**12**
PR	1 (8.3%)
SD	11 (92%)
DCR at 8 weeks	12 (100%)
PD	0
Not evaluable (N)	**2**

Large randomized Phase 3 studies of a) everolimus vs. placebo (Motzer 2010), b) nivolumab vs. everolimus (Motzer 2015a), and c) cabozantinib vs. everolimus (Choueiri 2015), all in predominantly the second line setting, have shown a PFS for everolimus of approximately 3.8 – 4.9 mo (see Figure 9.6-1, Panel A).

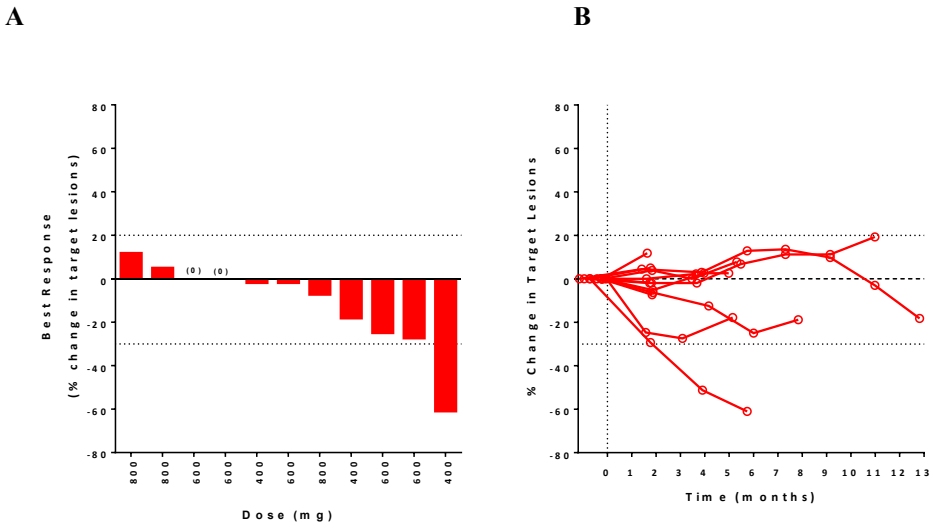

Figure 9.6-1. Best tumor response, and duration of tumor response for ccRCC patients receiving CB-839 + everolimus in Phase 1. A) Waterfall plot of best change in tumor burden, and B) Spider plot of tumor burden over time.

9.7 Rationale for CB-839 Dose Selection

CB-839 will be administered at the Recommended Phase 2 Dose (RP2D) of 800 mg BID determined from the Phase 1 dose escalation study of CB-839 + everolimus. Notably, no dose limiting toxicity was reported at this dose level, and the combination regimen was well tolerated with no maximum tolerated dose (MTD) determined for CB-839 with everolimus. In total the 800 mg dose of CB-839 has been administered with good tolerability as monotherapy to 22 patients with a variety of solid tumors and to an additional 25 patients in combination therapy with SOC agents (everolimus, paclitaxel, nivolumab and azacitidine). As noted above, in pharmacokinetic studies, exposures at the 800 mg RP2D and the minus-one dose (600 mg) 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 mg and 800 mg. However, all patients treated at the 800 mg dose demonstrated ≥ 90% target inhibition in platelets whereas

approximately 20% of patients treated at the 600 mg dose level showed target inhibition less than 90%. In aggregate these data support the risk: benefit ratio of the 800 mg CB-839 dose level.

10.0 PROCEDURES

This section describes evaluations to be performed during the different treatment periods of this study. All patients must sign an IRB 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/ EC policies. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent.

10.1 Screening

To determine a patient's eligibility patients will undergo required screening evaluations as outlined in Attachment 1. All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRF). Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

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 and it is not an anti-cancer therapy. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the appropriate eCRF, including the reason for treatment, name of the drug, dosage, route, and start and stop dates of administration.

Non-protocol systemic anti-cancer 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 unevaluable and assigned a censoring date or progression date.

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.

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of the multidrug efflux pump P-Glycoprotein (PgP). Per everolimus prescribing information, strong inducers and inhibitors CYP3A4 should be avoided (Attachment 6). Refer to the most current everolimus prescribing information appropriate to the respective site location about potential drug interactions and dosage adjustments suggested for co-administration with moderate inhibitors of CYP3A4 and/or PgP.

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, CB-839 should be taken 2 hours before antacid therapy.

10.1.2 Screening Evaluation

An IRB/IEC-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 C1D1.

The following screening assessments must be performed **within 21 days** before study drug administration on C1D1 according to the Schedule of Study Assessments in Attachment 1[with the exception of imaging (CT/MRI); scans performed within 28 days of study drug administration on C1D1 are acceptable]. Procedures listed below that are performed as part of

the normal standard of care and within 21 days prior to C1D1 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 with corrected QT interval by Fridericia's Formula (QTcF)
- Urinalysis, coagulation, HbA1c, and triglyceride and total cholesterol levels: these assessments should be repeated periodically during the course of the study as clinically indicated
- Clinical laboratory evaluation (serum chemistry, and hematology); see Attachment 1 and Attachment 2.
- Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to C1D1.
- Radiographic evaluation of tumor burden comprising diagnostic quality CT with intravenous contrast or MRI with contrast that is appropriate for RECIST 1.1 assessment (Attachment 5). For patients who cannot receive intravenous CT contrast, non-contrast CT of the chest with contrast enhanced MRI of the abdomen and pelvis is acceptable. Scans performed within **28 days prior to C1D1** will be accepted and do not need to be repeated (Attachment 1).
- Optional tumor biopsies may be collected from patients who sign a separate tumor biopsy informed consent form.
- Archival tumors, if available, will be collected all patients.

A patient who meets all of the inclusion criteria will be randomized and enter the study. Screen failures will be marked in the electronic data capture (EDC) system.

10.2 Randomization

Patients eligible after completing all screening evaluations will be randomly assigned in a 2:1 ratio to receive CBE or PboE.

Randomization will be stratified by the following factors:

- Number of prior VEGFR-targeting TKI therapies: 1 vs. >1
- Number of risk factors per Memorial Sloan-Kettering Cancer Center prognostic criteria for previously treated patients with RCC (Motzer 2004): favorable vs. intermediate/poor risk

Randomization should occur as close as possible to the planned start of treatment (ie, within 24 hours prior if practicable but no more than 3 days). Patients are defined as enrolled in the study if randomized. Patients who signed consent and are screened but never randomized are screen failures.

Crossover between treatment arms will not be allowed.

10.3 Study Treatment Procedures

For the complete list of schedules and 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.

Clinic visits for safety evaluations will occur on Cycle 1 Day 1 and Cycle 1 Day 15, then on day 1 of Cycles 2-12. Starting with cycle 13, safety evaluations will occur every 3 cycles, or more frequently as clinically indicated. The final 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 CT with intravenous contrast or MRI) will occur at Screening and approximately every 8 weeks after study initiation for the first 12 cycles, or more frequently as clinically indicated. After 12 cycles, tumor burden will be evaluated every 3 cycles or more frequently as clinically indicated.

10.4 Long Term Follow Up

Because the primary endpoint in this study is PFS, patients who discontinue study treatment for reasons other than progressive disease or death should continue to be followed by imaging per protocol schedule until documentation of progressive disease, death, withdrawal of consent, or initiation of a new anti-cancer treatment. Patients who are post-progression and in long term survival follow-up should be contacted every 3 mo for the first 12 mo following study discontinuation and then once every 6 mo thereafter. All reasonable efforts must be made to contact patient and report their ongoing status. This includes follow up with persons authorized by the patient.

10.5 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive either CB-839, placebo, or everolimus 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, and reason(s) for screen failure into the EDC system. Serious Adverse Event information will also be captured in the EDC.

10.6 Procedure Details

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

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

After randomization, safety assessments will be performed on day 1 of every cycle for the first 12 cycles. Starting with cycle 13, safety assessments will be performed on day 1 of every 3 cycles. More frequent safety evaluations may be performed if clinically indicated or at the

discretion of the Investigator. Unscheduled visits may be performed at any time and all should be recorded in the EDC. All AEs will be recorded from the time the patient receives the first dose of study drug up to 28 days after the last dose.

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 anti-cancer 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 End of Treatment. Symptom-directed physical exam are required as clinically indicated.

The Karnofsky performance status (Attachment 4) will be assessed during screening to determine the eligibility and the prognostic risk score according the MSKCC prognostic criteria (Motzer 2004). The Karnofsky performance status will be used to evaluate the patients' performance at the beginning of every cycle and at the end of treatment.

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 3-5 min prior to obtaining vital signs.

10.6.4 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. ECGs may be performed periodically as clinically necessary.

When performed, the ECG must be reviewed, by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate

eCRF. ECG results will include heart rate (HR), R-R interval (RR), PR interval, QRS interval, QT interval, and QTcF interval. The corrected QT interval will be corrected for respiratory rate according to the following formula:

$$\text{Fridericia's formula: } QTcF = QT/RR^{0.33}$$

10.6.5 Laboratory Assessments

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

To confirm eligibility, urinalysis, coagulation, HbA1c, and triglycerides, and total cholesterol will be performed at screening. These assessments should be repeated periodically during the course of the study as clinically indicated. Any clinically significant results should be entered in the EDC.

10.6.6 Patient-Reported Quality of Life Assessment

Patients will be asked to complete two health related quality of life 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). These questionnaires will be completed on day 1 of every cycle for the first 12 cycles then every 3 cycles starting with cycle 13 and at the End of Treatment.

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 and return it to the site either during the next visit or should send it to the site by fax or mail. Upon completion, the site should carefully review for completeness.

These assessments should be completed regardless of whether study treatment is given, reduces, held or discontinued.

10.6.7 Tumor Assessments

Radiographic response and disease progression will be determined using RECIST version 1.1 and should employ diagnostic quality CT with intravenous contrast or MRI scans (see Attachment 5 for methods of assessment discussion of CT and MRI).

Radiographic tumor assessments will include Chest/ Abdomen/ Pelvis (CAP). Diagnostic quality CT (or MRI) of chest/abdomen/pelvis with intravenous contrast will be performed for all patients at screening, every 8 weeks (±5 days) from C1D1 for the first 12 cycles, and every 12 weeks (± 7 days) beyond 12 cycles on study. For patients deemed intolerant of intravenous CT contrast, a non-contrast CT of the chest may be obtained along with a contrast enhanced MRI of the abdomen and pelvis.

To ensure image consistency, the same imaging modality and acquisition protocols used at screening should be used for subsequent tumor assessments.

For the purpose of patient management and treatment decisions, radiographic response and disease progression will be assessed by investigators using RECIST v1.1 (Attachment 5). Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study therapy if the patient is tolerating treatment, and repeat radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

10.6.8 Tumor Biopsies

10.6.8.1 Optional Fresh Tumor Biopsies

Optional tumor biopsies for exploratory biomarker assessment may be collected at any point on this study with patient consent. Biopsies should not be obtained from target lesions being followed for disease assessment.

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.

10.6.8.2 Archival Tumor Biopsies

Archival surgical 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 tissues collected from recent time points before enrollment is optimal because it more accurately reflects the current state of the tumor/microenvironment at the time of study entry.

10.6.9 Pharmacokinetic Samples

PK samples will be collected from all patients. Plasma PK samples will be used to measure concentrations of CB-839. Blood samples for PK analysis will be collected at the following time points:

- Cycle 1, Day 15: Pre-dose and 2 hours post dose(± 30 minutes)
- Cycle 2, Day 1: 4 hours and 6 hours post dose (± 1 hour). Patients can take their morning dose at home and PK samples can be drawn at the indicated times after dosing in the clinic.

The actual time of collection must be noted in the source documents and eCRFs. In the event that there is a delay in dosing on PK days, the PK sample should be collected during the next visit that the patient is in the clinic. On Cycle 1 Day 15, patients will have to arrive at the clinic and get their pre-dose PK sample drawn prior to taking their dose. On Cycle 2 Day 1, patients must record the time they take their morning dose and report to the site. This information will be entered in the EDC. Refer to the laboratory manual for details on collection kits and sample processing.

The plasma samples will be analyzed for CB-839 by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to Good Laboratory Practices (GLPs).

11.0 POTENTIAL TOXICITIES, DOSE MODIFICATION AND MANAGEMENT OF TOXICITIES

11.1 Potential Toxicities

11.1.1 CB-839

The most frequent adverse events (AEs) considered possibly or probably related to CB-839 monotherapy dosed on the BID schedule on the CX-839-001 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 9.5-2).

11.1.2 Everolimus

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections (see everolimus Package Insert). Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (CTCAE Grade 1-2). Everolimus has been associated with a low incidence of severe and potentially lethal AEs, including non-infectious pneumonitis, infections, and renal failure (see Warnings and Precautions in the Package Insert). Everolimus dosing and toxicity should be managed according to the Package Insert and local institutional practice.

11.1.3 CB-839 + Everolimus Combination

In a cohort of 19 patients treated during the Phase 1 evaluation of CB-839 + everolimus, the most frequent adverse events (AEs) considered possibly or probably related to one or both drugs were decreased appetite, hyperglycemia, and anemia (see Table 9.5-3). These have been primarily Grade 1/2 AEs.

The only Grade 3/4 AEs considered possibly or probably related to either CB-839 or everolimus or both drugs in more than 1 patient was hyperglycemia, which occurred in 2 patients, both with pre-existing diabetes (see Table 9.5-4).

11.2 Dose Modifications and Toxicity Management

The safety and tolerability profile of CB-839 is summarized above (Section 9.5). In general, management of AEs related to CB-839 and everolimus includes withholding the medication for moderate to severe toxicities and providing the appropriate supportive care.

The safety and tolerability profile of everolimus is well defined and outlined in the everolimus Package Insert. Per Package Insert, monitoring of fasting serum glucose and lipid profile is recommended prior to the start of everolimus therapy and periodically thereafter, as well as management of metabolic AEs with appropriate medical therapy. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. When possible, optimal glucose and lipid control should be achieved before starting a patient on everolimus.

11.2.1 Dose Modification Guidelines

Patients will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose delay) will be based on specific laboratory and AE criteria. Guidelines for dose modifications due to hematological and non-hematological AEs are provided in Tables 11.2-1 and 11.2-2, respectively. The dose levels for CB-839 dose reduction are provided in Table 11.2-3. For everolimus dose reduction levels, the most up the most up-to-date everolimus Package Insert applicable to the site location should be consulted and followed.

These dose modification guidelines provided in Tables 11.2-1 and 11.2-2 are based on the Package Insert for everolimus (dated September 2017) and the clinical experience with CB-839 and the combination to date. These guidelines are intended primarily for toxicities that are not easily managed with routine supportive care. Because everolimus prescribing information may change over time, the most up-to-date everolimus Package Insert applicable to the site location should be consulted and followed.

Table 11.2-1: Dose Modifications Guidelines for Hematologic Toxicity

Toxicity Grade (CTCAE v4)	Management of toxicity	CB-839 or Placebo	Everolimus
Hematologic: Grade 3/4 (other than those highlighted below)	Supportive care, as necessary	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline	Hold everolimus and resume at the same dose level upon resolution to ≤ Grade 1 or baseline. If toxicity recurs at Grade 3, hold and restart at the next lower dose
Grade 3/4 neutropenia or thrombocytopenia	Supportive care, as necessary	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline	Hold everolimus and resume at one dose level lower upon resolution to ≤ Grade 1 or baseline

Table 11.2-2: Dose Modifications Guidelines for Non-Hematologic Toxicity

Toxicity Grade (CTCAE v4)	Management of toxicity	CB-839 or Placebo	Everolimus
Non-hematologic clinically significant: (other than those highlighted below) Grade 2	Initiate appropriate medical therapy and monitor	If symptom not tolerable, hold and resume at the same dose level upon recovery to ≤ Grade 1 or baseline. If toxicity recurs, hold and restart at next lower dose.	If symptom not tolerable hold everolimus and resume at same or next lower dose level upon recovery to ≤ Grade 1. If toxicity recurs at Grade 2, hold and restart at next lower dose.
Non-hematologic clinically significant: (other than those highlighted below) Grade 3	Initiate appropriate medical therapy and monitor	Hold and resume at the same dose level or the next lower dose level upon recovery to ≤ Grade 1 or baseline.	Hold everolimus and resume at the next lower dose level upon recovery to ≤ Grade 1. If toxicity recurs at Grade 3, consider discontinuation.
Non-hematologic clinically significant: (other than those highlighted below) Grade 4	Initiate appropriate medical therapy and monitor	Permanently discontinue	Permanently discontinue everolimus
Non-infectious pneumonitis Grade 1	Monitor by CT at least every 3 cycles.	Continue	Continue everolimus.
Grade 2	Rule out infection and consider treatment with corticosteroid until symptoms improve to ≤Grade 1.	Hold and resume at the same dose level upon recovery to ≤ Grade 1 or baseline.	Hold everolimus and resume at the next lower dose level upon recovery to ≤ Grade 1 or baseline.

Toxicity Grade (CTCAE v4)	Management of toxicity	CB-839 or Placebo	Everolimus
Grade 3	Rule out infection and consider treatment with corticosteroid until symptoms improve to ≤Grade 1.	Hold and resume at the same dose level upon recovery to ≤ Grade 1 or baseline.	Hold everolimus and resume at the next lower dose level upon recovery to ≤ Grade 1 or baseline. If toxicity recurs at Grade 3, then consider discontinuation.
Grade 4	Rule out infection and consider treatment with corticosteroid until symptoms improve to ≤Grade 1.	Hold and resume at the same dose level upon recovery to ≤ Grade 1 or baseline.	Permanently discontinue everolimus
Stomatitis Grade 2	Manage with topical analgesic mouth treatments as per everolimus Package Insert and local practice.	Consider holding. If held resume at the same dose upon recovery to ≤ Grade 1	Hold everolimus and resume at the same dose level upon recovery to ≤ Grade 1. If toxicity recurs at Grade 2 hold and resume at next lower dose level upon recovery to Grade 1
Stomatitis Grade 3	Manage with topical analgesic mouth treatments as per everolimus Package Insert and local practice.	Hold and resume at the same dose or the next lower dose upon recovery to ≤ Grade 1	Hold everolimus and resume at the next lower dose upon recovery to ≤ Grade 1
Stomatitis Grade 4	Manage with topical analgesic mouth treatments as per everolimus Package Insert and local practice.	Hold and resume at the next lower dose upon recovery to ≤ Grade 1	Permanently discontinue everolimus
Metabolic events (e.g. hyperglycemia, dyslipidemia) Grade 1-2	Manage with appropriate medical therapy.	Continue	Continue
Metabolic events (e.g. hyperglycemia, dyslipidemia) Grade 3	Manage with appropriate medical therapy	Hold and resume at the same dose level or one dose level lower upon recovery to ≤ Grade 1 or baseline	Hold everolimus and resume at next lower dose level upon recovery to ≤ Grade 1 or baseline.
Metabolic events (e.g. hyperglycemia, dyslipidemia) Grade 4	Manage with appropriate medical therapy	Hold and resume at one dose level lower upon recovery to ≤ Grade 1 or baseline	Permanently discontinue everolimus

Table 11.2-3: Dose Reductions for CB-839 (or Placebo)

Dose Reductions of CB-839 or Placebo		
Dose Level	CB-839 Dose	Number of Tablets CB-839 or Placebo
Starting dose	800 mg BID	4
First dose reduction	600 mg BID	3
Second dose reduction	400 mg BID	2
Third dose reduction	Discontinue CB-839 or Placebo	0

11.2.2 Resumption of Study Treatment

For everolimus and CB-839 (or placebo), treatment may be delayed for up to 6 weeks from the last dose. Delays longer than 6 weeks are allowed only in cases where the delay was due to a non-drug related cause. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 4 weeks, the Medical Monitor must be consulted. Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

Upon withholding study drugs for adverse events, the study drugs may be restarted when the AE has returned to ≤ Grade 1 or baseline. In cases in which a particular toxicity is clearly related to only one of CB-839 or everolimus, the study drug that is not involved in causing the AE may be restarted prior to a return to ≤ Grade 1 or baseline. If CB-839 (or placebo) is restarted after permanent discontinuation of everolimus, CB-839 or placebo should be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in everolimus discontinuation.

11.3 Missed Doses

Missed doses of CB-839 or everolimus should be skipped. If a patient forgets to take a dose of CB-839 or everolimus and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed to skip that dose and NOT to take extra study drug at their next administration.

11.4 Discontinuation of Treatment and Withdrawal of Patients

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, disease progression, adverse events, patient request, withdrawal of consent, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor.

In unusual 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 PD may be considered in consultation with the medical monitor.

When a patient discontinues or is withdrawn, the Investigator will notify the Sponsor (or designee) and should perform all End of Treatment and follow up procedures as indicated in the schedule of study assessments (Attachment 1) after discontinuation of study drug. *Note that patients who discontinue study treatment for reasons other than progressive disease or death should be followed by imaging per protocol until progressive disease, death, initiation of a new anti-cancer therapy, or withdrawal of consent for study follow-up*.

12.0 TEST ARTICLE/STUDY DRUG

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 or placebo will be administered only to patients who have signed and dated an Informed Consent Form. Doses will be administered 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 or 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 should be taken 2 hours before antacid therapy. See Section 10.1.1 for discussion of acid suppression therapy.

Patients who vomit their CB-839 or placebo dose should be instructed NOT to make up that dose and to report the frequency of vomiting occurrences associated with study drug administration to the site.

Everolimus Tablets

Everolimus will be administered to patients who have signed and dated an Informed Consent Form. 10 mg everolimus will be administered on Days 1 through 28 of each 28-day cycle and should be taken orally QD around the same time every day. Administer either consistently with food or consistently without food. Everolimus dosing will not be adjusted for body weight or surface area.

12.2 Packaging and Labeling

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

Everolimus Tablets are available as 2.5, 5, or 10 mg strengths. Please refer to the everolimus Package Insert for specific instructions on packaging and labeling.

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

12.3 Storage and Stability

CB-839 Tablets or Placebo Tablets

CB-839 HCl Tablets or placebo tablets will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature, between 15 - 30ºC (59 - 86ºF).

Patients will be requested to store CB-839 or placebo at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

Everolimus Tablets

Everolimus should be stored at 15 - 30ºC (59 - 86ºF). Protect from light by storing in the

original package until time of use. For procedures for the proper handling, storage, preparation and administration of everolimus, please refer to the everolimus Package Insert.

12.4 CB-839 Accountability, Reconciliation, and Return

On Day 1 of Cycle 1, patients will be provided with enough study treatment (everolimus, CB-839 or placebo) 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 or placebo tablets remaining from the previous visit will be counted and recorded.

The Investigator or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to the Sponsor at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/ or bottles destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

If evidence of tampering is observed, notify the Sponsor and return the questionable CB-839 or placebo shipment with the appropriate form to the contract distribution center. Returned/ partially used, and unused CB-839 test article or placebo control article may also be destroyed and documented at the investigative site in accordance with approved site/institution standard operating procedures. If the investigative site does not have an approved standard operating procedure, investigative product may be returned to the distribution center for destruction.

12.5 Test Article Compliance

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

Missed doses of CB-839 or placebo should be skipped. If a patient forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed NOT to take extra study drug at their next administration.

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 and refractory ccRCC. Patients will be randomized to either the CB-839 with everolimus or to placebo with everolimus in a 2:1 ratio. The primary endpoint of this Phase 2 study is progression free survival (PFS) assessed by investigator per RECIST 1.1. The key secondary endpoint is overall survival (OS). Patients will be stratified by: a) prior VEGFR targeting TKI therapy (1 vs. > 1) and b) MSKCC Prognostic Criteria for Previously Treated Metastatic RCC (favorable vs. intermediate/poor risk)

14.2 Analysis Patient Sets

14.2.1 Efficacy Analysis Patient Set

The modified intention-to-treat (mITT) patient set will be the basis for the primary efficacy analysis for this study. The mITT set comprises all randomized patients who receive at least one tablet of any study-specific treatment (CB-839, placebo, or everolimus). With a double-blind design, patients who drop out before receiving any treatment are not influenced by the unknown treatment assignment. Therefore, the exclusion of such patients does not introduce bias to the between-arm patient balance. Patients in the mITT set will be analyzed according to the

treatment group to which they are randomized regardless of post randomization protocol deviations.

14.2.2 Safety Analysis Set

All patients who receive at least 1 tablet of any study-specific treatment (CB-839, placebo or everolimus) will be included in the analysis of safety and analyzed according to the actual treatment received. Patients randomized to the placebo arm having taken any dose of CB-839 will be analyzed in the CB-839 with everolimus combination arm.

14.3 Efficacy Analysis

14.3.1 Primary Efficacy Endpoint: Investigator-Assessed PFS

The primary efficacy endpoint is PFS defined as the time from randomization to the earlier of disease progression or death due to any cause. Radiographic disease progression will be assessed using the RECIST 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 radiographic disease assessment if any of the following scenarios occur:

- Patient is alive and progression free at the time of analysis data cutoff
- Disease progression or death occurs after missing data [including a non-evaluable (NE) status for overall response assessment] for two consecutive radiographic disease assessments
- Patient receives non-protocol RCC treatment prior to documentation of disease progression
- Patient is missing baseline disease assessment (censored at date of randomization)

The primary inferential comparison between the two treatment arms will use the log-rank test stratified by the randomization stratification factor for risk profile [MSKCC Prognostic Criteria for Previously Treated Metastatic RCC (favorable vs. intermediate/poor risk) and number of prior therapies with a TKI (1 vs. > 1)]. A 1-sided log-rank $p < 0.2$ will be regarded as a positive

sign in favor of the CB-839 + everolimus experimental treatment. The experimental over control hazard ratio will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. Kaplan-Meier curves will be presented with median estimates to visually display the disease progression distributions.

14.3.2 Secondary Efficacy Endpoints

Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause. For patients alive at 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.

14.3.3 Additional Endpoints

Overall Response Rate (ORR)

ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria. Response confirmation is not required in this double-blind protocol. Patients with no 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 14.4.1 conventions regarding PD censoring will apply. Response duration will be descriptively presented by Kaplan Meier curve and median estimate for responders in each treatment arm.

Disease Control Rate (DCR)

DCR is defined as the summed percentage of patients with CR, PR and SD according to RECIST 1.1 criteria documented at least 8 weeks following treatment initiation.

Patient Reported Outcomes

Subjects 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). Details of the planned analyses for these outcomes will be provided in the SAP.

14.3.4 Exploratory Analyses

To explore the effects of the following baseline factors, a multivariate Cox model regression analysis will be conducted for PFS. The model will include treatment arm as an independent variable with the following variables as covariates. Univariate plots will also be presented for descriptive purposes.

- Race (Caucasian vs. all others)
- Sex (male vs. female)
- Age (18–65 vs. > 65 years)
- Number of previous TKI therapies (1 vs. >1)
- Favorable vs. intermediate/poor risk prognosis group
- No prior immunotherapy vs. prior immunotherapy

14.4 Safety Analysis

Safety will be assessed by the incidence and severity of adverse events (AEs); the analysis will be performed on the Safety Analysis Patient Set as defined in Section 14.4.2.

Adverse events will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of patients reporting a given AE will be tabulated by treatment group according to the worst severity reported. Separate tables will be constructed for a) all reported AE's, b) serious AEs (SAEs), and c) AE's leading to permanent discontinuation of study treatment. The above tables will also be presented for treatment-emergent AEs (TEAEs) judged to be related to the study treatment.

14.5 Sample Size Estimation

A median PFS of 3.7 mo is estimated for the everolimus control group based on published data for 3rd line treatment of advanced ccRCC. The published data include non-randomized everolimus-specific PFS (Heng 2015), PFS across the 3rd line setting for all commonly used

agents (ibid.), and results from a Phase 3 randomized 3rd line study of dovitinib vs. sorafenib (GOLD study, Motzer 2014). In total across the IMDC database and the randomized GOLD study, these data represent 1490 unique patient outcomes specific to the 3rd line setting.

The proposed study of CBE vs. PboE will enroll patients with a 2:1 randomization between experimental and control arms with an accrual period of 8 mo and additional follow-up of 6 mo. If the control arm PFS is 3.7 mo and the true PFS hazard ratio of experimental patients to control patients is 0.60, the study will require approximately 42 experimental patients and 21 control patients in order to reject the null hypothesis of equal PFS between the two treatment arms with a power of 0.80. This estimation assumes a 1-sided type I error rate of 0.2, uniform accrual, exponential PFS distributions and the log-rank test for PFS comparison. The expected total PFS event count is 48 under the above assumptions.

15.0 Adverse Events

Single agent CB-839 has been well tolerated in three different Phase 1 clinical trials. For safety information on CB-839, refer to Section 9.5 above and to the most recent version of the Investigator's Brochure. For safety information on everolimus, refer to the everolimus Package Insert.

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 (NOTE: see definition below)
- 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. However, 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 a serious adverse event (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:

AEs 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 information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- 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 mo after completion of the study treatment must also be reported to the Investigator.

- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE
- Abuse (e.g., use for nonclinical reasons) with or without an AE

15.2 Recording and Reporting

After informed consent, but prior to initiation of study drug, only SAEs caused by protocol-mandated interventions (i.e., a protocol-related SAE such as a biopsy) will be collected.

Patients will be followed for AEs or SAEs from the time the patient initiates treatment with the study regimen up to 28 days after the last dose or until the start of a new treatment, whichever occurs first. 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 treatment, or in case of permanent impairment, until the condition stabilizes.

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

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 1 business day 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 Institutional Review Board (IRB) or Independent Ethics Committee (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.

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 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.

20.2 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.

20.3 Pre-Study Documentation

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

- Completed and signed form 1572
- 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
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure form for the Principal Investigator and any other persons listed in the 1572
- 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. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

20.4 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 AUTHORSHIP AND ACCOUNTABILITY

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
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily
CBE	CB-839 plus everolimus combination treatment
C_{cr}	Creatinine Clearance
ccRCC	Clear Cell Renal Cell Carcinoma
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeters
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete remission
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP, CYP450	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
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
g/dL	Grams per deciliter
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HbA1C	Glycated Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate

Abbreviation or Term[1]	Definition/Explanation
hr	Hour or hours
ibid	The same reference as above
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous, intravenously
kg	Kilogram
KPS	Karnofsky Performance Score
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
mcL/ µL	Microliter
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Miligram
mL	Milliliter
mo	Months
MOA	Mechanism of Action
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
mTOR	Mechanistic Target of Rapamycin
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall response rate
OS	Overall Survival
PboE	Placebo tablets plus everolimus treatment
PD-1	Programmed Cell Death protein 1
PD-L1	Programmed Death Ligand 1
PgP	P-Glycoprotein
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PPI	Proton Pump Inhibitors
PR	Partial response

Abbreviation or Term[1]	Definition/Explanation
PSA	Prostate Specific Antigen
PT	Prothrombin time
QD	Once-daily dosing
QTcF	Corrected QT interval, Fridericia's formula
RP2D	Recommended Phase 2 Dose
RBC	Red Blood Cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
Scr	Serum Creatinine
SD	Stable disease
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time of maximum observed concentration
TEAE	Treatment-emergent adverse event
TID	Three times daily
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor

1 This may not be a comprehensive list of all abbreviations in this document. All of these abbreviations may or may not be used in this document.

23.0 REFERENCES

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ATTACHMENT 1: SCHEDULE OF STUDY ASSESSMENTS

(1 cycle = 28 days)	Pre-randomization	Post-randomization				
Visit	**Screening[1]**	**Cycle 1**		**Cycle 2+**	**Cycle 13+ (Every 3 cycles) [13]**	**End of Treatment/ Follow up**
Assessments	≤ 21 days prior to C1D1	Day 1[2] (≤3 days post randomization)	Day 15 (± 2 days)	Day 1 (± 5 days)	Day 1 (± 7 days)	EOT: Within 28 days post treatment discontinuation
Written Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics and Medical History	X					
Physical Examination[3]	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X
Karnofsky Performance Status	X	X		X	X	X
12-lead ECG with QTcF	X					
Urinalysis[5]	X					
HgA1c levels[5, 6]	X					
Triglyceride and total cholesterol levels[5, 7]	X			X		
Coagulation tests[5]	X					
Serum Chemistry levels	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
Serum or Urine Pregnancy Test[8]	X					X
Pharmacokinetic (PK) Assay[9]			X	X		
CB-839 or Placebo Dosing		CB-839 or Placebo will be administered twice daily (BID) with food				
Everolimus Dosing		Everolimus will be administered once daily (QD) at the same time every day.				
Optional Tumor Biopsy	Can be collected any time on study. Patients must sign the optional tumor biopsy consent					
Archival Tumor Collection	X					

(1 cycle = 28 days)	Pre-randomization	Post-randomization				
Visit	**Screening[1]**	**Cycle 1**		**Cycle 2+**	**Cycle 13+ (Every 3 cycles) [13]**	**End of Treatment/ Follow up**
Assessments	≤ 21 days prior to C1D1	Day 1[2] (≤3 days post randomization)	Day 15 (± 2 days)	Day 1 (± 5 days)	Day 1 (± 7 days)	EOT: Within 28 days post treatment discontinuation
Radiographic Evaluation of Tumor Burden (diagnostic CT with intravenous contrast or MRI)[10]	X[11]			Every 8 weeks	Every 12 weeks	X
Quality of Life Questionnaires		X		X	X	X
Adverse Events		Document new or worsening AEs from time of first dose through 28 days after study treatment discontinuation. AE information will be collected at study visits and may also be collected via any other forms of communication or by subject report. Certain AEs and SAEs that are ongoing 28 days after study discontinuation are to be followed until resolution or determination by the investigator that the event is stable or irreversible.				
Concomitant Medications	Document concomitant medication taken from time of informed consent through 28 days after study treatment discontinuation.					
Follow up						X[12]

Explanation of Superscripts

1. Results of screening assessments must be reviewed before randomization to confirm that the patient meets all eligibility criteria. An IRB/IEC-approved Informed Consent Form (ICF) must be signed and dated ≤42 days prior to C1D1.
2. Assessments on C1D1 should be completed prior to first dose of study treatment unless otherwise indicated.
3. Complete physical exam is required at Screening and at End of Treatment. A symptom-directed physical exam can be done on all other visits. System exams are only required as clinically indicated
4. Vital sign measurements include temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure.
5. Assessment completed at screening. Investigators should monitor during the study if it is deemed necessary per everolimus Package Insert
6. Investigators should periodically monitor fasting glucose as per everolimus Package Insert.
7. Triglycerides should be repeated at Cycle 2 (+/-5days). Total cholesterol levels are required at baseline only.
8. Required for all females of child-bearing potential. Screening pregnancy test must occur within 3 days prior to C1D1.
9. Samples are collected on C1D15: pre-dose and 2 hrs post dose and on C2D1: 4 hrs and 6 hrs post dose. Refer to the laboratory manual for detailed instructions on samples kits, collection, and shipment to a central laboratory.
10. Imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the patient's participation in the study.
11. Tumor assessments within 28 days prior to C1D1 will be accepted.
12. Patients will be contacted every 3 mo for the first 12 mo then every 6 mo thereafter to confirm survival.
13. Starting with Cycle 13, assessments will be completed every 3 cycles (12 weeks). More frequent visits should be completed if clinically indicated.

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

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

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

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

Urinalysis

- Protein
- Glucose
- Ketones
- Hemoglobin
- Nitrite
- Leukocyte esterase
- pH
- Specific gravity
- Urobilinogen
- Microscopic evaluation(performed at the discretion of the Investigator based on results of routine urinalysis or as clinically indicated)

ATTACHMENT 3: MSKCC PROGNOSTIC SCORE

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 MSKCC prognostic score.

Parameter	Risk Factor	Criteria Value	Patient Value	If Patient Value meets criteria, enter 1
KPS	Low PS	< 80%		
Corrected Calcium*	High Corrected Calcium	≥ 10 mg/ dL		
Hemoglobin	Low Hemoglobin	Males: ≤ 13 g/dL Females: ≤ 11.5 g/dL		
			Sum total= MSKCC Prognostic Score:	

*Corrected Calcium = ([4 – serum albumin in g/ dL] x 0.8 + serum calcium)

Risk Group Based on MSKCC Prognostic Score

Risk Group	MSKCC Prognostic Score
Favorable- Risk	0
Intermediate- Risk	1
Poor- Risk	2 or 3

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

Source: Eisenhauer 2009

Sponsor's Note: 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 recommended to be 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: leptomeningeal disease, 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 subjected 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.

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

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. 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**.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

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.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an

additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

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

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

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.

When patients have non-measurable (therefore non-target) disease only, Table B is to be used.

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.

Best overall response: All time points

The best overall response (Table C) will be determined by statistical programming once all the data for the patient are known.

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

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

Table B: Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

2. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table C: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

3. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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.

Conditions that define 'early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

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. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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 Everolimus

Per the everolimus Package Insert, everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

In healthy subjects, compared to everolimus treatment alone there were significant increases in everolimus exposure when everolimus was co-administered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - Cmax and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4/PgP should not be used.

Use caution when everolimus is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the everolimus dose.

Agents That May Decrease Everolimus Blood Concentrations

CYP3A4/PgP Inducers

In healthy subjects, co-administration of everolimus with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, decreased everolimus AUC and Cmax by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of everolimus when co-administered with strong CYP3A4/PgP inducers if alternative treatment cannot be administered.

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 <u>the past 7 days.</u>**

		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
RCC2	I have had blood in my urine	0	1	2	3	4

D
R
S-
P

DRS-E	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

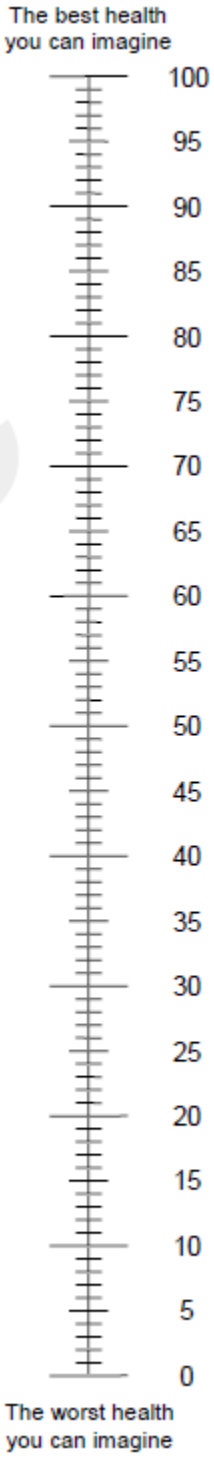
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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: AMENDMENT 2 SUMMARY OF CHANGES

The major changes and rationale for Amendment 2 are listed below:

1. **Section 8.1.2f and 9.1**: Inclusion criteria for prior treatment has been revised to remove the specific requirement for PD on the most recent VEGF TKI and to remove the requirement for prior cabozantinib or nivolumab. Patients are required to have received at least 2 prior lines of therapy and have received at least one VEGF TKI and have progressive disease on or after the most recent therapy and within 6 mo of C1D1 on the ENTRATA study.
    a. **Rationale:** the original protocol inadvertently excluded late-line and treatment-refractory patients who our investigators feel should be eligible for this study. This change opens the study to patients who have treatment refractory disease even if the most recent TKI was discontinued for toxicity or intolerance, so long as the patient has progressive cancer on the most recent therapy and within 6 mo of C1D1 on ENTRATA. Also the requirement for prior treatment with cabozantinib or nivolumab was for the ENTRATA study when it specifically had registrational intent. The current study which is focused on detection of activity beyond everolimus alone does not require that language.

2. **Section 8.2.1b**: Exclusion criteria for washout period from completion of any anticancer therapy was changed for TKI and investigational therapy to be within 2 weeks or 5 half-lives, whichever is longer.
    a. **Rationale:** to allow a minimum time of 2 weeks for a TKI therapy or investigational therapy to be washed out.

3. **Section 10.1.2 and Attachment 1**: Screening evaluations amended to allow patients to sign the informed consent form ≤42 days prior to C1D1.
    a. **Rationale:** to not restrict the time from signing the informed consent form to C1D1.

4. **Section 10.3:** Clinic visits for safety evaluations will occur on Cycle 1 Day 1 and Cycle 1 Day 15 then during day 1 at Cycles 2 – 12. Starting with Cycle 13, safety evaluations will occur every 3 cycles, or more frequently as clinically indicated. The final assessment will occur at the End of treatment visit.
    a. **Rationale:** the requirement for weekly visits during Cycle 1 was condensed to be consistent with standard of care visits.

5. **Section 11.3:** If CB-839 and everolimus doses were skipped outside of ± 6 hr then it should not be made up.
    a. **Rationale:** clarified to include everolimus as well as CB-839.

6. **Section 12.1:** CB-839 should be taken **2 hours before** antacid therapy.
    a. **Rationale:** to clarify the appropriate time interval between CB-839 drug administration if a patient is receiving antacid therapy.

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Reason for signing: Approved	Name: Sam Whiting Role: Clinical Development Date of signature: 07-Aug-2018 22:10:25 GMT+0000

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