Winship Protocol #: Winship4643-19

TITLE: ***A Phase 2 Study of Neoadjuvant Cabozantinib in Patients with Locally Advanced Non-metastatic Clear Cell Renal Cell Carcinoma***

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

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1 BACKGROUND INFORMATION

In the United States in 2016, approximately 60,000 patients were diagnosed with renal cell carcinoma (RCC) with 20,000 diagnosed or developing metastatic disease (1). The majority of patients, 80-85%, have clear-cell renal cell carcinoma (ccRCC) with the remainder comprised of variant histology renal cell carcinoma subtypes. Metastatic RCC is a heterogeneous disease with variable clinical outcome. Advances in understanding of both genetic mutations of or silencing of the tumor suppressor gene, von Hippel-Lindau (VHL) gene, have shown that this abnormal gene produces a deviant protein that causes the accumulation of hypoxia inducible factors (HIFs). These in turn induce the production of products that are critical to the proliferation of ccRCC, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and transforming growth factor-alpha (TGF-α). All four of these cellular products, i.e., HIF, VEGF, PDGF and TGF-α, constitute rational targets for the development of novel therapies. The relative ease of administration of recently developed oral targeted therapies has led to their use in patients with their primary renal tumor in place, most commonly in poor surgical candidates and patients with unresectable primary renal tumors (2-5).

Cabozantinib (XL-184) is a recently developed small molecule inhibitor of the tyrosine kinases c-Met, AXL and VEGFR2 that has been shown to reduce tumor growth, metastasis, and angiogenesis (6). In a metastatic, heavily pre-treated ccRCC population, cabozantinib (XL-184) was evaluated in a single-arm phase I trial enrolling 25 patients with the majority having intermediate-risk disease by MSKCC risk criteria (7). The ORR was 28% and an additional 52% had stable disease. The median PFS was 12.9 months, which was very favorable compared with other targeted agents. The phase III METEOR study randomized 658 patients to cabozantinib versus everolimus after front line anti-angiogenic therapy. The median PFS was 7.4 months versus 3.8 months in favor of cabozantinib satisfying the primary endpoint of the trial (8). The co-primary endpoint of improvement in overall survival was also achieved with a median OS of 21.4 months for patients randomized to cabozantinib compared to 16.5 months for those randomized to everolimus (HR 0.66 [95%CI 0.53-0.83]; p =0.00026) (8). Subgroup analyses of OS according to MSKCC risk group were consistent with the results for the overall population. The most common grade 3 or 4 adverse events included hypertension (49 [15%] in the cabozantinib group vs 12 [4%] in the everolimus group), diarrhea (43 [13%] vs 7 [2%]), fatigue (36 [11%] vs 24 [7%]), palmar-plantar erythrodysesthesia syndrome (27 [8%] vs 3 [1%]), anemia (19 [6%] vs 53 [17%]), hyperglycemia (3 [1%] vs 16 [5%]), and hypomagnesemia (16 [5%] vs none) (8). Serious adverse events grade ≥ 3 occurred in 130 (39%) participants in the cabozantinib group and in 129 (40%) in the everolimus group (8). One treatment-related death occurred in the cabozantinib group (death; not otherwise specified) and two occurred in the everolimus group (1 aspergillus infection and 1 pneumonia aspiration) (8). These findings led to the FDA approval of cabozantinib in the second line setting for patients with metastatic renal cell carcinoma.

In the randomized phase II CABOSUN trial, patients were randomized to cabozantinib versus sunitinib as the initial treatment of patients with metastatic clear cell renal cell carcinoma with intermediate or poor risk disease (9). Patients randomized to receive cabozantinib had an improved median PFS of 8.2 versus 5.2 months for those assigned to sunitinib (HR 0.66 [95%CI 0.46 to 0.95]; p=0.012) (9). ORR was 46% (95% CI, 34 to 57) for cabozantinib vs 18% (95% CI,

10 to 28) for sunitinib (9). Median OS was 30.3 months for cabozantinib vs 21.8 months for sunitinib (adjusted HR 0.80, 95% CI 0.50, 1.26) (9). All-causality grade 3 or 4 adverse events were 67% for cabozantinib and 68% for sunitinib and included diarrhea (cabozantinib, 10% v sunitinib, 11%), fatigue (6% v 15%), hypertension (28% v 22%), palmar-plantar erythrodysesthesia (8% v 4%), and hematologic adverse events (3% v 22%) (9). Treatment-related Grade 5 events occurred in 3 participants in the cabozantinib arm (acute kidney injury, sepsis, and jejunal perforation) and 3 participants in the sunitinib arm (sepsis, respiratory failure, and vascular disorders) (9). Later analysis showed that cabozantinib treatment significantly prolonged PFS per dependent radiology review committee compared with sunitinib as initial systemic therapy for advanced RCC of poor or intermediate risk (10). Cabozantinib was subsequently approved by the United States Food and Drug Administration (FDA) in April 2016 for the treatment of RCC. Recently, FDA approval of cabozantinib was extended to the first line setting for the treatment of RCC.

Potential advantages of neoadjuvant therapy include downsizing and/or downstaging of tumors to change surgical approach from radical to partial nephrectomy or from open to minimally invasive surgery, and to allow for resection of unresectable tumors and potentially sparing organs. Lane et. reported presurgical sunitinib in 72 patients with renal cell carcinoma (11). Median tumor size improved from 7.2 cm to 5.3 cm after sunitinib treatment. Downsizing occurred in 65 tumors (83%), with 15 partial responses (19%) (11). 41% of patients with nephrometry score >9 could undergo partial nephrectomy, and eGFR change was -16% in partial nephrectomy group vs -24% in radical nephrectomy group (11). Rini et al. reported a phase II study of pazopanib in patients with localized renal cell carcinoma (12). 6 out of 13 patients for whom partial nephrectomy not possible at baseline underwent successful partial nephrectomy (12). Karam et al reported neoadjuvant axitinib in biopsy proven locally advanced clear cell renal cell carcinoma patients. In this cohort, all patients were T3a, and received up to 12 weeks of axitinib without any grade 3-4 adverse events. 11/24 patients achieved partial response, 13/24 patients achieved stable disease, and no disease progression were observed. The increased response rates for cabozantinib in mRCC above, along with the neoadjuvant axitinib data where 45% of neoadjuvantly treated patients achieved partial response, strongly support an expanded role for cabozantinib in the neoadjuvant setting.

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are as follows:

Primary objective:

- To assess the objective response rate (complete and partial responses), following the administration of cabozantinib for 12 weeks in patients with locally advanced biopsy-proven non-metastatic ccRCC prior to undergoing surgery.

Secondary Objectives:

- To assess the safety, and tolerability of neoadjuvant cabozantinib.
- To determine the clinical outcome (DFS, OS) of patients with non-metastatic ccRCC who treated with neoadjuvant cabozantinib.
- To evaluate the surgery related outcomes.
- To evaluate correlative studies, including biomarkers, quality of life, and frailty/sarcopenia assessment of patients with non-metastatic ccRCC who are treated with neoadjuvant cabozantinib.

3 STUDY DESIGN

Patients with renal cell carcinoma with clear cell component will be enrolled to receive neoadjuvant cabozantinib for 12 weeks before surgical resection. If patients are eligible and want to to be part of the study, the patients will participate for up to 3 years.

Each subject's course will consist of four periods:

- A Pre-Treatment Period in which subjects are consented and undergo screening assessments to be qualified for the study (Section 5.1);
- A Treatment Period in which subjects receive study treatment and undergo study assessments. This period will end at the time of completion of cabozantinib, or when the patient withdraws consent or experiences unacceptable toxicity (Section 5.2);
- A Post-Treatment Period in which subjects no longer receive study treatment and undergo kidney surgery (Section 5.3). This period also includes intraoperative and post-operative period.
- A Long-Term Follow-up Period in which subjects will be follow after surgery (Section 5.4)

Study Treatment Discontinuation

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Section 6.3.2;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects of childbearing potential who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

4 STUDY POPULATION

4.1 Inclusion Criteria

A subject must fully meet all of the following criteria to be eligible for the study:

1. Patients with renal mass consistent with a clinical stage ≥ T3Nx or TanyN+ or deemed unresectable by surgeon;
2. Renal cell carcinoma with clear cell component on pre-treatment biopsy of the primary tumor;
3. The subject is ≥ 18 years old on the day of consent;
4. ECOG performance status ≤1
5. Patients must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
    - Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support.
    - White blood cell count ≥ 2500/mm3 (≥ 2.5 GI/L).
    - Platelets ≥ 100,000/mm3 (≥ 100 GI/L) without transfusion.
    - Hemoglobin ≥ 9 g/dL.
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 x upper limit of normal (ULN). ALP ≤ 5 x ULN with documented bone metastases.
    - Total bilirubin ≤ 1.5 x ULN (for subjects with Gilbert's disease ≤ 3 x ULN).
    - Serum albumin ≥ 2.8 g/dl.
    - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 40 mL/min (≥ 0.67 mL/sec) using the Cockcroft-Gault equation:
        - Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)
        - Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85
    - Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol).

6. No hormonal therapy, chemotherapy, immunotherapy, or any other systemic therapy for a malignancy, in the 5 years prior to current study enrollment;
7. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment;
8. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons;
9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.

4.2 Exclusion Criteria

1. Evidence of metastatic disease on pre-treatment imaging.
2. The subject has received of any type of cytotoxic, biologic or other systemic anticancer therapy for kidney cancer;
3. The subject has received any other type of investigational agent within 28 days before the first dose of study treatment;
4. Known brain metastases or cranial epidural disease.
5. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel). Allowed anticoagulants are the following:
    - Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
    - Low-dose low molecular weight heparins (LMWH) are permitted.
    - Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
6. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 14 days before the first dose of study treatment.
7. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    - Cardiovascular disorders:

- Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
- Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
- Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism) within 6 months before first dose.

- Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
  - The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, active inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
  - Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.

    Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
- Clinically significant hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose.
- Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
- Other clinically significant disorders that would preclude safe study participation.
  - Serious non-healing wound/ulcer/bone fracture.
  - Uncompensated/symptomatic hypothyroidism.
  - Moderate to severe hepatic impairment (Child-Pugh B or C).

8. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.'
9. Prolongation of the QTcF interval defined as > 500 msec per electrocardiogram (ECG) within 28 days before first dose of study treatment.

   Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the

initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.

10. Pregnant or lactating females.
11. Inability to swallow tablets.
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
13. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy. Patients with Gleason 6 (3+3) prostate cancer with previous treatment or on active surveillance may also be allowed on protocol.

4.3 Screen Failures

Subjects who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, will not be enrolled into the study and are considered screen failures. All subjects which have signed informed consent, and were deemed ineligible will be recorded in a log with the reason of ineligibility and their enrollment status will be updated in OnCore. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, eligibility criteria, study discontinuation date, adverse events and any serious adverse event (SAE).

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Pre-Treatment Period

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. The following assessments will be conducted before subjects receive their first dose of cabozantinib on this protocol:

- Baseline renal biopsy with pathologic confirmation of renal cell carcinoma with clear cell component
- A cross sectional CT of the chest with or without contrast

- An MRI of the brain with and without contrast
- Cross sectional imaging of the abdomen/pelvis which can be CT with IV contrast or MRI with and without contrast
- Urinalysis and UPCR
- TFTs (TSH, free T3, free T4)
- Echocardiogram or MUGA if clinically indicated
- Urine pregnancy Test for female patients with child bearing potential
- Baseline laboratory values including CBC with differential, platelets, electrolytes, BUN, Cr, AST, ALT, bicarbonate, total bilirubin, fractionated bilirubin, lipase, γ-glutamyltransferase (GGT), glucose, phosphorous, magnesium, amylase, INR/PT, albumin, bilirubin, alkaline phosphatase, C reactive protein, urinalysis, urine protein to creatinine ratio
- A baseline ECG 12-lead
- A baseline history and physical by physician
- Assessment of baseline height and weight
- Documentation of baseline adverse events from any previous therapies
- Documentation of baseline performance status

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

5.2 Treatment Period

During the Treatment Period subjects will receive cabozantinib for 12 weeks or until the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 3. Subjects should be instructed to immediately inform the investigator or study team member of any AEs.

The following schedule of assessments applies to all subjects (Table 5-1). More frequent assessments should be obtained if clinically indicated.

Table 5-1: On Study Assessments

	Study Treatment Period			Post-Treatment Period	Long-Term follow up Period
	Screening[a]	Week 1 Day 1[m]	Week 2, 6 Day 1 (± 5 days)	Within 14 days after last dose	
Informed consent	X				
Demographics	X				
Medical and cancer history/demographics	X				
Physical examination	X	X	X	X	
Height	X				
Weight	X	X	X	X	
Vital signs	X	X	X	X	
ECOG performance status	X	X	X	X	
Clinical laboratory tests [b]	X	X	X	X	
Urinalysis and UPCR	X	X	X[c]	X	
PT/INR, PTT	X	X	X[c]		
TFTs (TSH, free T3, free T4)	X		X[c]	X	
12-lead ECG	X	X	X[c]	X	
ECHO or MUGA[j]	X				
Cabozantinib administration		X (daily)	X (daily)		
Urine Pregnancy test[l]	X	X	X[c]	X	
Tumor assessment[d]	X		X[c]	X[n]	X[e]
Concomitant medications		X	X	X	
Adverse events	Continuous			X	
Follow-up				X	X[f]
Blood for correlative studies		X	X[c]	X	X[k]
Pathologic Confirmation of clear cell component	X				
Quality of life questionnaires[h]		X	X[c]	X	
Frailty assessment[i]		X	X[c]	X	
Sarcopenia assessment		X	X[c]	X	
Kidney Surgery				X[g]	

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PT/INR, prothrombin time/International Normalized Ratio; PTT, partial prothrombin time, TFT, thyroid function test; UPCR, urine protein/creatinine ratio

[a] Screening will be done within 28 days before the 1st dose.

[b] aboratory tests should include a standard hematology panel (CBC, differential, platelets) and chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase [GGT], glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total protein). CRP

[c] Week 6 only

[d] All sites of known disease must be assessed.

[e] Surveillance scan after surgery will be obtained per investigator.

[f] Patients in long term follow-up can be seen by medical oncology or urology team, have chart reviewed, or phone call to determine current status every 3 months. (+/- 14 days).

[g] Patients will undergo kidney surgery min 28 days after the last dose of cabozantinib.

[h] Appendix C

[i] Appendix D

[j] If clinically indicated

[k] Blood collection post-surgical resection for correlative studies

[l] Only from female patients with child bearing potential within 72 hours of study drug

[m] These assessments may be done within 14 days of Week 1 Day 1, prior to releasing the cabozantinib.

[n] This scan can be done within 28 after last dose of cabozantinib

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Regular tumor assessments should be performed in accordance to the guidelines in Section 5.5 to determine if PD is present.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

5.3 Post-Treatment Period

Subjects will return to the study site within 14 days after their last dose of cabozantinib to complete end-of-study assessments. Laboratory, imaging and physical examinations will be performed. Remaining study treatment will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

This period includes intraoperative and post-operative assessments. Patients will wait a minimum of 28 days (washout period) from the last dose of cabozantinib prior to surgical resection. Patients will be assessed for intraoperative and post-operative complications using the universally recognized Clavien Dindo perioperative classification of adverse events (13). Specifically, we will examine endpoints including, but not limited, chylous ascites, pulmonary embolism, ileus, bleeding, superficial wound descience, fascial dehiscence, pleural effusion, pneumonia, urinary retention, gastroparesis, anemia, and post- operative delirium. We will also collect data regarding procedure type, i.e. radical nephrectomy, partial nephrectomy, and rate of conversion from radical to partial nephrectomy.

5.4 Long Term Follow-up Period

After kidney surgery, patients will enter the long term follow-up period. Data to determine a patient's current status may be collected from clinic visits with either medical oncology or urology ,chart review, or phone call every 3 months (+/- 14 days) until disease recurrence, initiation of new antineoplastic or investigational therapy, whichever occurs first. During this period, surveillance imaging will be obtained per investigator. A final blood sample for correlative studies will be collected after surgery. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Long-term follow-up continues until the patient's withdrawal of consent or loss to follow up, death, or study termination.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

•The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

•Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

•Should the participant continue to be unreachable, patient will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.5 Laboratory Assessments

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hematocrit • platelet count • RBC count • hemoglobin	
Serum chemistry		
• albumin • ALP • amylase • ALT • AST • bicarbonate • BUN • chloride	• creatinine • GGT • Glucose (fasted) • calcium • lactate dehydrogenase • lipase • CRP	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Other		
• TSH, Free T3 and Free T4 • Pregnancy text (urine or serum) for women of child-bearing potential		• PT/INR or PTT

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate ; GGT, γ-glutamyltransferase; INR, International Normalized Ratio; PT, prothrombin time; PTT partial thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; UPCR, urine protein/creatinine ratio; WBC, white blood cell; CRP, C-reactive protein

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

5.6 Tumor Assessment

5.5.1 *Efficacy Assessments*

Objective response rate (ORR) is the primary endpoint for this study which will be evaluated using RECIST 1.1 criteria (14). Evaluation of response will follow the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). All tumor measurements must be recorded in centimeters.

For the purposes of this study, patients should be re-evaluated for response at 12 weeks. This will be obtained after last dose of cabozantinib before surgical resection while waiting 28 days wash-out period. In addition to week 12 scan, week 6 scan should also be obtained to rule out rapid progression. Only scans at week 12 (prior to surgery) will be used for purposes of the primary objective. In order to have better response assessment, we will use same type of scan at baseline and at 12 weeks. Since patients are required to be non-metastatic disease patients, likely only target lesion assessment will be needed.

- Target Lesions:

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lymph nodes must be at least 15mm in short axis to be included as a target lesion. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum of longest diameters will be used as the reference by which the objective tumor response is characterized.

- Non-target Lesions:

All other lesions (or sites of disease) should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

5.5.2 *Evaluation of Target Lesions:*

- Complete Response (CR):

The disappearance of all target lesions.

- Partial Response (PR):

At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

- Progressive Disease:

At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

- Stable Disease:

Insufficient shrinkage to qualify for partial response, or insufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

5.5.3 *Evaluation of Non-target Lesions:*

- Complete Response:

The disappearance of all non-target lesions.

- Incomplete Response/Stable Disease:

The persistence of one or more non-target lesion(s)

- Progressive Disease:

The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

- Evaluation of Best Overall Response: (see table below)

Evaluation of Best Overall Response (RECIST)

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-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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 the objective progression even after discontinuation of treatment.

6 TREATMENT PROCEDURES

6.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

6.1.1 *Investigational Treatment: Cabozantinib*

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 60-mg tablets are oval and the 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 6-1.

Table 6-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

[a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose

Refer to the Pharmacy Manual for details on storage and handling of cabozantinib.

6.2 Cabozantinib Administration

Subjects will receive cabozantinib orally at a (starting) dose of 60 mg once daily.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day for total of 12 weeks. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 6.3 below.

6.3 Cabozantinib Dose Modifications, Interruptions, and Discontinuation

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 60 mg/day. 2 dose reduction levels of cabozantinib are permitted (see Table 6-2).
- Dose modification criteria for cabozantinib are shown in Table 6-3. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 6-3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.
- Dose interruptions for reason(s) other than related AEs (eg, surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Guidelines for the management of specific AEs are provided in Section 6.3.3.

Table 6-2: Dose Reductions of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
60-mg cabozantinib oral qd	40-mg cabozantinib oral qd	20-mg cabozantinib oral qd
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	No dose reduction permitted
20-mg cabozantinib oral qd	No dose reduction permitted	—

qd, once daily
Cabozantinib will be discontinued if a qd dose of 20-mg cabozantinib (minimum dose) is not tolerated

Table 6-3: Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.4.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 6.3.2. For re-treatment criteria of study treatment after a dose hold see Section 6.3.1.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

6.3.1 *Cabozantinib Dose Reinstitution and Reescalation*

If the subject recovers from his or her toxicities to CTCAE v.4.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 6-2 for the schedule of dose reductions).

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 60 mg/day) may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

6.3.2 *Guidelines for Management of Potential Adverse Events*

Subjects will be monitored for AEs from the time of signing informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician or other study team member immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

6.3.3 *Cabozantinib*

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

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs (eg, deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

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

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Section 6.3).

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

6.3.3.1 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects should be instructed to notify their physician or other study team member immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 6-4. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

Table 6-4: Management of Diarrhea Associated with Cabozantinib

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

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

6.3.3.2 Non-Gastrointestinal Fistula

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

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

6.3.3.3 Hemorrhage

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

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

6.3.3.4 Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

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

6.3.3.5 Hypertension

Table 6-5 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 6-5: Management of Hypertension Associated with Cabozantinib

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

BP, blood pressure.

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

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

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

6.3.3.6 Stomatitis and Mucositis

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

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

6.3.3.7 Skin and Subcutaneous Tissue Disorders

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

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

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

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

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

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

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

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

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

6.3.3.8 Osteonecrosis

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

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

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

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

6.3.3.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 6-7 provides treatment guidelines for proteinuria deemed related to cabozantinib.

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

Table 6-7: Management of Proteinuria Associated with Cabozantinib

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

RCC, renal cell carcinoma; UC, urothelial carcinoma; UPCR, urine protein/creatinine ratio.

6.3.3.10 Nervous System Disorders

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

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

6.3.3.11 Hepatocellular Toxicity

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (eg, liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

Cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 × ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib should be interrupted until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate drug-induced liver injury (DILI). Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.

6.3.3.12 Infections

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

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

6.3.3.13 Blood and Lymphatic System Disorders

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

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as

transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

6.3.3.14 Fatigue

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

6.3.3.15 Weight Loss

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

6.3.3.16 Corrected QT Prolongation

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

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

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

If the average QTcF from the three ECGs is > 500 ms, the following actions must be taken:

- Interrupt cabozantinib treatment
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)

- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

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

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved

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

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

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose

6.3.3.17 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 6.3 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

6.3.3.18 Endocrine Disorders

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

6.3.3.19 Angioedema

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

7 CONCOMITANT MEDICATIONS AND THERAPIES

7.1 Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 6.3.3.8). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
  - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
  - *Therapeutic doses of LMWH* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 6 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.
  - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 6.3.3.4.
  - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction).
  - For restrictions on oral anticoagulants see Section 7.2.

Potential drug interactions with cabozantinib are summarized in Section 7.3.1.

7.2 Prohibited or Restricted Therapy

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

- Any investigational agent or investigational medical device.
- Oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).
- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

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

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

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

7.3 Potential Drug Interactions

7.3.1 *Potential Drug Interactions with Cabozantinib*

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

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

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

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

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

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

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

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.

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

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

7.4 Study Treatment Accountability

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

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

8 SAFETY

8.1 Adverse Events and Laboratory Abnormalities

8.1.1 *Adverse Events (AEs)*

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in in Section 6.

All untoward events that occur after informed consent through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE).

8.1.2 *Serious Adverse Events (SAEs)*

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

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

- Result in death;
- Is life-threatening (i.e., in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);

- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.
- Results in persistent or significant disability or incapacity:
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

Reporting:

8.1.3 *Relationship to Study Treatment*

Assessment of the relationship of the AE to the study treatment by the investigator is based on the following two definitions:

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;
- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

8.1.4 *Serious Adverse Event Reporting:*

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be promptly documented on an SAE Report Form and in the electronic database (OnCore). All SAEs must be assessed by PI in order to determine reporting criteria to regulatory authorities

and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures, from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs that are assessed by the PI as **related** to drug or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

8.1.5 *Regulatory Reporting*

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;
- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.
- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the study-supporter of a clinical trial. The PI shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the sponsor to disseminate these updates to participating PIs.

8.2 Other Safety Considerations

8.2.1 *Laboratory Data*

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay or requirement for additional medication or monitoring) or that is considered

to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

8.2.2 *Pregnancy/Lactation Exposure*

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

8.2.3 *Medication Errors/Overdose*

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

8.2.4 *Follow-Up of Adverse Events*

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur more than 30 days after the decision to discontinue study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

9 STATISTICAL CONSIDERATIONS

The primary outcome is objective response rate (complete and partial responses) at week 12 after the administration of cabozantinib. The Simon's two-stage design will be adopted for a possible early termination for futility. We hypothesize that there is > 24% response rate at 12-week and a rate < 5% will be considered as futility. In the first stage, 11 patients will be accrued (this does not include screen failures), and if there is no responses among them, the study will be stopped for futility. Otherwise, additional 6 patients will be accrued for a total of 17 patients. The null hypothesis will be rejected if there are 3 or more responses in 17 patients. The design yields a type I error rate of 0.05 and power of 80% when the true response rate is 24%. The final response rate will be estimated with 95% confidence interval by binomial test.

The safety profile of the treatment will be documented and summarized by summary statistics as frequency and percentage for each AE. We will do safety assesment after the first 6 patients without pausing the enrollment.

For disease free survival (DFS), which was defined as the interval between time of surgery and the first tumor recurrence, or death. Patients will be censored at time of last follow-up. For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. Overall survival (OS) and disease free survival (PFS) will be estimated

with the Kaplan-Meier method. The DFS and OS of each patient group at specific time points, such as 6 months, 1 year, and 3 year, etc. will be also estimated alone with 95% CI.

For the biomarker study, descriptive statistics will be first used to summarize biomarker endpoints, including analyses of tumor biopsies. Biomarker data will also be displayed graphically, where appropriate. Depending on whether data is normally distributed, t-test or Wilcoxon rank sum test will be used to compare each biomarker between any two groups stratified by response or other factors, respectively. Logistics regression model will be further employed to test the adjusted effect of biomarker on the response rate after adjusting for other factors.

10 DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within

Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Dr. Bilen and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety. During the meetings the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being included on delegation of authority log. All AE and SAE will be handled according to Section 8.2 which provides detailed instructions on reporting requirements.

11 STUDY COMMITTEES

N/A

12 ETHICAL ASPECTS

12.1 Local Regulations

The study must fully adhere to the principles with the FDA GCP (Good Clinical Practice). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

12.2 Informed Consent

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

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

12.3 Institutional Review Board/Ethics Committee

This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulation

s. The investigator will send a letter or certificate of IRB/EC approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

12.4 Correlative studies

Paired tissue will be collected at baseline from all 17 patients either archival tissue or within 28 days before Week 1 day 1 after consent is signed. Tissue will be obtained during surgery as post treatment. The obtained tissues will be handled in the following way:

1) RNAlater for RNA stabilization and tissue storage
2) Formalin-fixed paraffin block with one cut H&E stained slide
3) Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate-controlled storage room that is temperature (less than 27ºC) and humidity controlled.

Tissue will be evaluated using IHC or immunofluorescence to measure relevant immune markers (i.e. CD3, CD4, CD8, CD163, PD-1, PD-2, PDL-1, MIF, TAM and stromal/ vascular markers, MET, others). When sufficient quantities of fresh tissue is available, it will also be dissociated and flow cytometry will be used to determine the phenotypic characteristics of cell populations in the tumor microenvironment. Tissue will be preserved for future exploratory studies including genomic profiling.

Peripheral blood samples

Approximately 60 mL of peripheral blood will be collected prior to initiation of study therapy (at baseline), week 6 day 1 (+/-5 days), the completion of treatment prior to surgery and post-surgical resection (Table 5-1). The peripheral blood mononuclear cells will be isolated from these samples and stored in -80°C freezers until analysis. Plasma will be stored in -80°C freezers until analysis.

Samples will be evaluated including but not limited to:

i. Determine whether there are phenotypic changes in of T-cell or myeloid cell surface markers (including co-stimulatory/immune checkpoint molecules) in PBMCs after treatment.

ii. Determine whether functional changes are evident in PBMCs in response to treatment and whether these data correlate with clinical outcome measures. Pending quantity of cells a variety of assays may be performed, including but not limited to intracellular cytokine production and expression of CD107.

iii. Assess ctDNA quantity and analysis in plasma samples at baseline and the completion of treatment prior to surgery.

Shipping and handling instructions

After appropriate processing, the blood samples, tissue blocks, slides or frozen tissue samples will be sent to:

Kissick Laboratory

1462 Clifton Rd, Room 420

Atlanta, Georgia, 30322

ph: 617 259 8364

email: haydn.kissick@emory.edu

On the day that the specimens are to be shipped, notify Dr. Haydn Kissick of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

Research blood contact Information:

Kissick Laboratory

ph: 617 259 8364

email: haydn.kissick@emory.edu

Quality of life will be studied using the Functional Assessment of Cancer Therapy-Kidney Specific Index-19 (FKSI-19) questionnaire (Appendix C), which will be filled out at baseline, on weeks 6, and 12 after treatment initiation.

Frailty assessment will be studies using the Fried Frailty score (Appendix D), which will be obtained at baseline, on week 6, and 12 after treatment initiation.

Sarcopenia assessment will be done by using baseline and week 12 scans via SliceOmatic v5.0 by TomoVision program.

13 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the principal investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

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

14 CONDITIONS FOR TERMINATING THE STUDY

At any time, the study may be terminated by the investigator, the IRB, or by Exelixis. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual

study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practical.

15 STUDY DOCUMENTATION AND RECORD-KEEPING

15.1 Investigator's Files and Retention of Documents

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

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

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of (a) 2 years following the marketing application approval date for the study treatment in the indication being investigated, or (b) 2 years after the investigation is completed or discontinued, or (c) for a period of time consistent with local regulatory requirements, whichever is longest. After that period, the documents may be destroyed subject to local regulations with prior written permission from Exelixis. If the investigator wants to assign the study records to another party or move them to another location, Exelixis must be notified in advance.

15.2 Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

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

15.4 Case Report Forms

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

16 MONITORING THE STUDY

Cumulative protocol- and patient-specific data will be submitted electronically into ONCORE monthly. Patients will be monitored per institutional standard.

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

18 PUBLICATIONS OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days before submission and also comply with any provisions regarding publication that are agreed to between the PI's institution (Emory University and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined in accordance to guidelines established by the International Committee of Medical Journal Editors.

19 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30.

2. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.

3. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-8.

4. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26(33):5422-8.

5. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010;28(13):2144-50.

6. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10(12):2298-308.

7. Choueiri TK, Pal SK, McDermott DF, Morrissey S, Ferguson KC, Holland J, et al. A phase I study of cabozantinib (XL184) in patients with renal cell cancer. Ann Oncol. 2014;25(8):1603-8.

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

9. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017;35(6):591-7.

10. Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018;94:115-25.

11. Lane BR, Derweesh IH, Kim HL, O'Malley R, Klink J, Ercole CE, et al. Presurgical sunitinib reduces tumor size and may facilitate partial nephrectomy in patients with renal cell carcinoma. Urol Oncol. 2015;33(3):112 e15-21.

12. Rini BI, Plimack ER, Takagi T, Elson P, Wood LS, Dreicer R, et al. A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma. J Urol. 2015;194(2):297-303.

13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

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

APPENDICES

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PILL DIARY

Cabozantinib Pill Diary

Subject Initials:___ Subject ID: _____

Instruction: Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Instructions:

Planned Daily Dose: ___ **mg**

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
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42				

Patient Signature: _____ **Date:** _____

This section to be completed by a Research Nurse / Research Coordinator:

Dosing Week Start Date: _____ Dosing Week End Date:_____

Lot Number: _____ # of Tablets Dispensed:_____

Any Interuptions? □ Yes □ No Any Dose reduction? □ YES □ NO

Comments:

APPENDIX C: QUALITY OF LIFE ASSESSMENT (NCCN-FACT FKSI-19 V2)

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	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
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	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

APPENDIX D FRAILTY ASSESSMENT

Fried frailty score	Explanation
Shrinking	Self-reported unintentional weight loss ≥10 lb in the last year.
Weakness	Measured by having the patient squeeze a hand-held dynamometer (Jamar). Three serial tests of maximum grip strength with the dominant hand were performed, and a mean of the 3 values was adjusted by sex and BMI. Men met the criteria for weakness if their BMI and grip strength were ≤24 kg/m^2 and ≤29 kg of force; 24.1 to 26 and ≤30 kg; 26.1 to 28 and ≤31 kg; >28 and ≤32 kg, respectively. Women met the criteria for weakness if their BMI and grip strength were ≤23 kg/m^2 and ≤17 kg; 23.1 to 26 and ≤17.3 kg; 26.1 to 29 and ≤18; and >29 and ≤21 kg, respectively.
Exhaustion	Measured by responses to questions about effort and motivation. The following 2 statements were used from the modified 10-item Center for Epidemiological Studies-Depression scale: "I felt that everything I did was an effort" and "I could not get going." Subjects were asked, "How often in the last week did you feel this way?" Potential responses were 0 = rarely or none of the time (<1 day); 1 = some or little of the time (1 to 2 days); 2 = a moderate amount of the time (3 to 4 days); and 3 = most of the time. Subjects answering either statement with a response of 2 or 3 met the criteria for exhaustion.
Low activity	Determined by inquiring about leisure time activities. Physical activities were ascertained for the previous 2 weeks using the short version of the Minnesota Leisure Time Activities Questionnaire, and included frequency and duration. Weekly tasks were converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure below the following criteria were classified as having low physical activity: men, <383 kcal/wk; women, <270 kcal/wk.
Slow walking speed	Measured by the speed at which a patient walks 15 feet. The final time was taken by averaging 3 trials of walking the 15 feet at a normal pace. Men met the slowness criteria if height and walk time were ≤173 cm and ≥7 seconds, or >173 cm and ≥6 seconds, respectively. Women met criteria if height and walk time were ≤159 cm and ≥7 seconds, or >159 cm and ≥6 seconds, respectively.

*Each domain yields a dichotomous score of 0 or 1, based on the criteria provided. Score classified patients as not frail (0 to 1), intermediate frail (2 to 3), and frail (4 to 5).