THE UNIVERSITY OF TEXAS MD
ANDERSON CANCER CENTER

DIVISION OF CANCER MEDICINE

An Observational Study of cabozantinib and Androgen Ablation in Patients with Androgen-Dependent Metastatic Prostate Cancer

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1.0 Objectives

Primary Objective(s) / Endpoint(s)
In this study, we will explore the safety and clinical efficacy of cabozantinib combined with androgen ablation in men with newly diagnosed androgen-dependent prostate cancer based on progression free survival. The primary end points are:

1. To assess the tolerance and safety of cabozantinib in combination with androgen ablation in this patient group.
2. To estimate the time to castrate-resistant progression defined by any of the following: (a) radiographic progression (using RECIST 1.1 for visceral disease and PCWG2 for Bone Scans), (b) receipt of additional anti-cancer therapy, or (c) clinical progression warranting discontinuation from the study as judged by the treating physician.
3. To collect and bank blood and tissue specimens for future hypothesis-generating studies.

Secondary Objective(s) / Endpoint(s)
Secondary endpoints will include:

1. Overall Survival
2. Radiologic responses
3. Biomarker modulation (for example PSA, CTC, serum cytokine profiles, bone specific alkaline phosphatase, urine n-telopeptides)
4. Tumor pharmacodynamic measures (molecular-pathologic analysis of c-Met/VEGFR signaling pathways using metastatic tissue samples).

2.0 Background

Cabozantinib (XL184) is a novel small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) that promote tumor cell proliferation and/or angiogenesis including RET, MET, VEGFR2/KDR, and KIT. In a recently reported phase II randomized discontinuation study of cabozantinib in patients with advanced solid tumors, a high proportion of patients with mCRPC achieved clinically significant responses while on therapy characterized by reductions in PSA, reductions in lymphadenopathy, reductions in pain, and improvement in bone scans(1). These results are attributed to the fact that overexpression of MET (and/or its ligand HGF) correlates with prostate cancer progression and the development of metastasis (2-4). Based on these encouraging results, a multi-center, non-randomized expansion (NRE) cohort for patients with mCRPC has been initiated. **We now propose to study the potential safety and benefit of cabozantinib in patients with metastatic androgen-dependent prostate cancer.**

The front-line paradigm for the treatment of metastatic androgen-dependent prostate cancer remains disruption of androgen receptor signaling (5). Despite reliable initial responses, however, all patients eventually develop castrate-resistant progression, a disease state responsible for 32,050 deaths last year in the United States (6, 7). Recent advances in tumor biology have elucidated growth-promoting pathways that contribute to the development of castrate-resistant disease. Importantly, these oncogenic pathways provide crosstalk between the “epithelial compartment” and the “stromal compartment” (8). For

example, stromal elements within bone – the most frequent organ site for prostate cancer metastases - promote the evolution of castrate-resistant disease. The rationale to disrupt this crosstalk has led to the discovery of drugs that target tumor stromal elements in additional to the cancer epithelial cell (9).

There is increasing evidence from data derived from primary human tumors and pre- clinical models that Met is a critical oncogenic pathway that contributes to the evolution of castrate-resistant disease. For example, Met is upregulated by removing androgens and the anti-proliferative effect of Met inhibitors is greater in castrate-resistant versus androgen-dependent cell lines (10, 11). Furthermore, the anti-tumor effect of Met inhibitors is greatly enhanced when combined with androgen ablation therapy in pre-clinical models (11). These results suggest the hypothesis that combining Met inhibition with androgen ablation will prevent (or delay) the development of castrate-resistant disease.

In the present study, we will explore this hypothesis by combining cabozantinib with androgen deprivation in patients with newly diagnosed, androgen-dependent metastatic disease. Data from our own institution suggest that the median time to progression (as defined by the development of castrate-resistant disease) in unselected patients treated with androgen ablation alone is approximately 24 months. However, in a subset of patients with "high-volume" disease (>3 bone lesions and/or visceral metastases), the median time to progression is 11.2 months (12).

3.0 Eligibility Criteria

Inclusion Criteria:

1. Histologic proof of prostate adenocarcinoma

2. Newly diagnosed Androgen-Dependent Prostate Cancer. Patients already on ADT are eligible as long as the time from initiation of LHRH analog or antagonist is not greater than 3 months.

3. Metastatic disease on bone scan and/or involvement of soft tissues (lymph nodes and/or viscera) by CT scan, PET/CT, or MRI

4. PSA > 1 ng/ml, unless anaplastic features are present (according to eligibility 10)

5. Life expectancy from a co-morbid illness > 3 years

6. ECOG performance status ≤ 2

7. Patients must have adequate organ function as defined by:
   - ANC ≥ 1,500/ul (unless due to bone marrow infiltration by tumor in which case ANC ≥500/ml are allowed)
   - Hgb ≥ 9 gm/dL (unless due to bone marrow infiltration by tumor in which case Hgb>8 gm/dL)
   - Total bilirubin ≤ 1.5times the upper limit of normal. For patients with known Gilbert's

disease, total bilirubin should be ≤ 3mg/dL

- platelet count ≥ 100,000/mm^3 (unless due to bone marrow infiltration by tumor in which case ≥50,000/ml are allowed)
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × ULN if no liver involvement, or ≤ 5 × ULN with liver involvement
- Lipase < 2 x the upper limit of normal
- Urine protein/creatinine ratio (UPCR) ≤ 1
- Serum phosphorus ≥ LLN
- estimated creatinine clearance of ≥ 40 ml/min.

8. Prior ADT is allowed if it was an adjunct to definite local therapy, was given for ≤ 1 year, and was completed at least 12 months before initiating therapy for metastatic disease.

9. Prior therapy with other TKI inhibitors or any other type of investigational agent is allowed if it was an adjunct to definitive local therapy, was given for ≤6 months, and was completed at least 12 months before initiating therapy for metastatic disease.

10. Patients with "anaplastic" features are eligible for this trial as defined by at least one of the following:
    a) Any of the following metastatic presentations: exclusive visceral metastases, radiographically predominant lytic bone metastases identified by plain X-ray or CT scan, bulky (>5 cm in longest dimension) lymphadenopathy or high-grade (gleason >8) tumor mass in the prostate/pelvis.
    b) Low PSA (≤ 10 ng/ml) at initial presentation (prior to androgen ablation or at symptomatic progression in the castrate-setting) plus high volume (≥20) bone metastases.
    c) Elevated serum LDH (≥ 2 x ULN) or elevated serum CEA (≥ 2 x ULN) in the absence of other etiologies.
    d) Short interval (≤ 180 days) to castrate-resistant progression following initiation of hormonal therapy.

11. 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 drug(s).

Exclusion Criteria:

1. Biological agents (antibodies, immune modulators, cytokines, or vaccines) or radionuclide treatment within 6 weeks of the first dose of study treatment.

2. Radiation therapy within 2 weeks prior to initiation of study treatment.

3. Symptomatic or uncontrolled brain metastasis or epidural disease requiring current treatment including steroids and anti-convulsant.

4. The subject has had another diagnosis of malignancy requiring systemic treatment within the last two years, unless non-melanoma skin cancer, or superficial bladder cancer.

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

   - Chronically uncontrolled hypertension, defined conventionally as consistent and repeated systolic pressures above 140 mmHg or diastolic pressures above 90 mmHg despite anti-hypertensive therapy. This may be better established with home BP readings than with clinic visit results. There is no criterion related to a specific BP result required for eligibility, nor are acute BP elevations that are related to iatrogenic causes, acute pain, or other transient reversible causes considered to be an exclusion criteria. The intent is to exclude patients with chronically uncontrolled hypertension that might be further exacerbated by Cabozantinib.

   - Other cardiovascular disorders such as symptomatic congestive heart failure (CHF), unstable angina pectoris, clinically-significant cardiac arrhythmias, history of stroke (including TIA, or other ischemic event) within 6 months of study treatment, myocardial infarction within 6 months of study treatment, history of thromboembolic event requiring therapeutic anticoagulation within 6 months of study treatment or main portal vein or vena cava thrombosis or occlusion.

   - Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
     - Any of the following at the time of screening

       a) intra-abdominal tumor/metastases invading GI mucosa b)

       active peptic ulcer disease,

       c) inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis

     - Any of the following within 6 months before the first dose of study treatment:

       a) history of abdominal fistula

       b) gastrointestinal perforation

       c) bowel obstruction or gastric outlet obstruction

       d) intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more that 6 months ago.

     - GI surgery (particularly when associated with delayed or incomplete healing) within 28 days. Note: Complete healing following abdominal

surgery must be confirmed prior to initiating treatment with cabozantinib even if surgery occurred more that 28 days ago.

- Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy or concurrent evidence of intraluminal tumor involving the trachea and esophagus.

6. The subject is unable to swallow tablets.

7. The subject has a previously-identified allergy or hypersensitivity to components of the study treatment formulation.

8. Oral corticosteroids ≥ 7.5mg prednisone (or prednisone equivalents).

9. Prior treatment with cabozantinib.

10. The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization.

4.0 Drug Information

4.1 Cabozantinib

Cabozantinib (XL184) is a new chemical entity that inhibits multiple RTKs with growth-promoting and angiogenic properties. The primary targets of cabozantinib are RET, MET, VEGFR2/KDR, and KIT (Table 1).

Table 1: Cabozantinib(XL184) IC50 Values in Biochemical, Enzymatic Assays

Kinase	IC50 (biochemical) [nM]
RET	3.8
MET	1.8
VEGFR2/KDR	0.035
KIT	4.6
ICSO, concentration required for 50 %target inhibition.	

Treatment with cabozantinib shows rapid effects on the tumor endothelium, resulting in breakdown of the vasculature beginning 24 hours after administration of cabozantinib, thus suggesting potent anti-angiogenic effects of cabozantinib. These effects translate into significant tumor growth inhibition after cabozantinib treatment in multiple tumor models including human medullary thyroid cancer (MTC), human breast cancer, human lung carcinoma, and rat glioblastoma. Overall, the data generated in vivo demonstrate that the target profile of cabozantinib translates to potent anti-angiogenic activity and potent anti-tumor efficacy.

4.1.1 Clinical Experience with Cabozantinib

As of 04 May 2011, 1003 subjects have been enrolled in open-label clinical studies of cabozantinib, and 330 subjects have been enrolled in a placebo-controlled blinded Phase 3 study. Clinical data are available from nine studies of cabozantinib including four Phase 1 studies, one Phase 1b/2 study, three Phase 2 studies, and one Phase 3 study. A summary of the availability of clinical data for cabozantinib, including the data sources and the dates of data cutoffs, is shown in the table below.

Study	Data Set	Number of Subjects	Cutoff Date
XL184-001	SAEs	85	04 May 2011
	Clinical database (AEs)	86[a]	01 March 2011
	Clinical database (antitumor activity)	85	16 April 2010
XL184-002	SAEs	26	04 May 2011
	Clinical database (AEs)	19	01 March 2011
	Clinical database (antitumor activity)	-	-
XL184-008	SAEs	23	04 May 2011
	Clinical database (AEs)	11	01 March 2011
	Clinical database (antitumor activity)	-	-
CA205-001 IXL184-014	SAEs	3	04May2011
	Clinical database (AEs)	3	01 March 2011
	Clinical database (antitumor activity)	-	-
XL184-201	SAEs	222	04 May 2011
	Clinical database (AEs)	214	01 March 2011
	Clinical database (antitumor activity)	105	28 April2010[b]
XL184-202	SAEs	93[c]	04 May 2011
	Clinical database (AEs)	77	01 March 2011
	Clinical database (antitumor activity)	54	01 March 2011
XL184-203	SAEs	531	04 May 2011
	Clinical database (AEs)	174[d]	01 March 2011[d]
	Clinical database (AEs)	490[d]	09May2011[d]
	Clinical database (antitumor activity)	490	09May2011
XL184-205	SAEs	19	04 May 2011
	Clinical database (AEs)	17	01 March 2011
	Clinical database (antitumor activity)		
XL184-301	SAEs	330	04 May 2011

AE, adverse event; SAE, serious adverse event.

a. One subject withdrew from and re-enrolled in XL184-001. This subject is counted once in enrollment, demographic tables, and SAE analyses (N = 85) and twice in adverse event analyses (N= 86).

b. Data available for Groups A and B.

c. Includes subjects treated with the combination of cabozantinib plus erlotinib as well as those treated with cabozantinib alone. One subject discontinued during the erlotinib Rum-In Stage and never received any dose of cabozautinib.

d. The summary of pooled adverse events presented in Section 5.4.1 includes data from 174 subjects

from Study XL184-203 as of the cutoff date of 01 March 2011 for the open-label l2-week Lead-In Stage; for Study XL184-203 only, an updated safety analysis based on data from 490 subjects (Lead-In Stage) as of the cutoff date of 09 May 2011 was also conducted for the RDT Cohorts of the study (see Section 5.1.7 for description of cohorts), and the safety profile was not significantly changed from the 01 March 2011 data cutoff. A separate AE summary table for Study XL184-203 as of 09 May 2011 is presented in Appendix D.

4.1.2 Clinical Safety Profile

The AE and SAE data summarized in the following sections include those reported and entered in the clinical database and safety database, respectively, as of 01 June 2010. The clinical studies with cabozantinib are ongoing, thus the AE data from the clinical database does not yet include all SAEs. Data from double-blinded studies is not presented. To date more than 561 subjects have been studied in open-label clinical trials with cabozantinib, including treatment with cabozantinib as a single agent, as well as cabozantinib in combination with temozolomide and radiation therapy, and cabozantinib in combination with erlotinib.

4.1.3 Adverse Events

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (eg, pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal [GI] perforation and rectal/perirectal abscess. Arterial thromboembolism (transient ischemic attack [TIA], myocardial infarction [MI]) have been reported rarely.

4.1.4 Serious Adverse Events

Out of all 561 subjects enrolled in open-label clinical trials with cabozantinib (XL184), 224 subjects (40%) experienced one or more SAEs, and 96 subjects experienced one or more SAE that was assessed to be related to treatment with cabozantinib. This total includes two late-breaking cases (one case of abdominal distension and failure to thrive in Study XL184-201 and one fatal respiratory failure in Study XL184-203) that were reported after the data cut- off. Across all open-label studies, the most commonly reported events, regardless of relationship to cabozantinib, were PE (in 21 subjects), convulsion (in 17 subjects), DVT (in 13 subjects), pneumonia (in 13 subjects), vomiting (in 12 subjects), abdominal pain (in 11 subjects), diarrhea (in 11 subjects), nausea (in 11 subjects), dehydration (in 10 subjects), and dyspnea (in eight subjects). The most commonly reported events across all open-label studies that were assessed as drug-related were PE (in 14 subjects), diarrhea (in nine subjects), DVT (in seven subjects), nausea (in seven subjects), hypertension (in five subjects), thrombocytopenia (in five subjects), dehydration (in four subjects), vomiting (in four subjects), abdominal pain (in three subjects), and perirectal abscess (in

three subjects). In addition, one late- breaking case of reversible posterior leukoencephalopathy syndrome (RPLS) was reported after the data cut-off in the double-blinded placebo-controlled Study XL184-301.

4.1.5 Deaths

A total of 52 deaths were reported within 30 days of the last dose of study drug; the majority was due to disease progression, and 5 deaths were assessed to be related to cabozantinib: GI hemorrhage (in one subject), PE (in two subjects), respiratory failure (in one subject), and hemoptysis (in one subject).

4.1.6 Clinical Pharmacokinetics

In Exelixis study XL184-001, in which doses are expressed in terms of their L-malate salt weight (see Appendix J for freebase weight equivalents), a preliminary PK analysis has been performed for 74 subjects. The cut-off date for the data used for this PK analysis is 02 September 2008. Pharmacokinetic results from Cohorts 1-9 (0.08-11.52 mg/kg, Intermittent 5&9, PIB) show that systemic exposure (Cmax and area under the plasma drug concentration time curve from time 0 to the last quantifiable concentration following dosing [AUC0-last]) values increased generally dose-proportionally with increasing cabozantinib dose. Terminal phase half-life (t1/2, z) values were long (range: 59.1 to 136 hours). Data from Cohorts 10-13 (175 mg qd PIB; 265 mg qd PIB; 175 mg qd capsule; 250 mg qd capsule) and Cohort 99 (175 mg qd capsule) show that drug accumulation (based on Cmax and AUC0-24 values) at steady-state after daily dosing is approximately 4- to 6-fold.

In addition, exposure values from PIB (Cohorts 10) or Capsule (Cohorts 12 and 99) are compared in Table 2. The data show that cabozantinib exposure (AUC) values from capsule cohorts are about 2.0 fold greater than those observed in the respective PIB cohort.

Table 2: Comparison of Exposure from PIB (Cohorts 10) or Capsule (Cohorts 12& 99)

	Day 19 Cmax (ng/mL)	**Day 19 AUC (ng×h/mL)**
Cohort 10 175 mga qd PIB, n = 3	1410	21200
Cohort 12 and 99 175 mga qd capsule, n = 19	2310	41600
AUC, area under the plasma drug concentration time curve; Cmax, maximum plasma concentration; PIB, powder in bottle; qd, once daily.		

Data from 18 subjects in XL184-201 (GBM) are available as of 26 January 2009. The data show that pre-dose concentration values at C1D15 are consistent with those reported in the Phase 1 setting: 1800 ± 868 ng/mL (n =18) versus 1920 ± 751 ng/mL (n = 16). In addition, the peak to trough concentration ratios at steady-

state are moderate, with a value approximately equal to unity.

Pharmacokinetic analysis of cabozantinib has not been studied in subjects receiving a capsule dose of 125 mg (salt weight) qd, but simulated exposure values are expected to be about 70% of those from 175 mg (salt weight). Based on the simulated data, exposure values from the 125-mg (salt weight) cohort or the 175-mg (salt weight) cohort are statistically different: 95% confidence interval for AUC values are 26399 ± 1022 vs. 37651 ± 1730 ng×h/mL, respectively. In addition, the simulated steady-state average concentration from cabozantinib at 125 mg (salt weight) is 1100 ng/mL.

4.1.7 Comparative Bioavailability Study of Cabozantinib Tablet and Capsule Formulations in Healthy Adult Subjects (Study XL184-005)

Study XL184-005 is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK. Based on the preliminary PK data from 23 subjects who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal- phase half-life ($t_{1/2,z}$) of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours. The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for the maximum plasma concentration (C_{max}) and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [$AUC_{0\text{-last}}$ or $AUC_{0\text{-inf}}$]: 40-43% for the tablet formulation, 43% for the capsule formulation.) The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

4.1.8 Effect of Food on the Bioavailability of Cabozantinib in Healthy Adult Subjects (Study XL184-004)

Study XL184-004 is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned

treatment of Test (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules 30 minutes after administration of a high-fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules under fasting conditions). Blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics.

Based on the preliminary PK data from 46 subjects who completed both treatments, a high-fat meal did not appear to alter the terminal $t_{1/2, z}$ of cabozantinib [mean $t_{1/2, z}$: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max} to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-}last}$ fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

4.1.9 Composition, Formulation, and Storage

At study sites, all study medication will be stored at room temperature. For additional information relating to the study drug formulation and composition, please see the current version of the investigator's brochure.

Destruction of Cabozantinib
If cabozantinib is to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

4.1.10 Investigational Treatment

Chemical Name: Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

4.1.11 Cabozantinib Tablets

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. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval. The components of the tablets are listed in Table .

Table 4-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

4.1.12 Storage Conditions

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigational product must be kept in a locked area with restricted access. The investigational product must be stored and handled in accordance with local regulations, labeling specifications, policies, and procedure.

The investigator or pharmacist will also keep accurate records of the quantities of the investigational products dispensed and used for each subject. The study monitor will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of all investigational product used.

4.2 Androgen Deprivation Therapy

A luteinizing hormone-releasing hormone (LHRH) analog or antagonist, such as Leuprolide (Lupron),Goserelin (Zoladex) or Degarelix (Firmagon) will be used as androgen deprivation therapy (ADT). Anti-androgens (such as bicalutamide) may be used for up to 4 weeks to prevent a “flare-response”.

5.0 Treatment Plan

All patients will receive androgen ablation therapy, either by means of luteinizing hormone–releasing hormone super-agonist (of any formulation), LHRH antagonist, or surgical castration. The use of anti-androgens to prevent a “flare-response” is permitted for up to 4 weeks at the discretion of the treating physician. Since patients with metastatic prostate cancer are typically started on hormonal therapy before being seen at M.D. Anderson, eligible patients may have received up to 3 months of androgen deprivation therapy prior to initiating cabozantinib. The time-to-progression data will be calculated from the start of hormonal therapy, not from the date of initiation of study drug

cabozantinib.

All patients will receive cabozantinib at a starting dose of 60mg PO q day. Study cycles will be 3 weeks in duration (+/- 3 days). All patients will stay on treatment as long as they are benefitting.

Patients will be removed from study if they meet any of the following criteria:

- Disease progression
- Unacceptable toxicity
- Patient decision to withdraw
- Palliative radiation involving more than one site
- In the judgment of the investigator, further treatment would not be in the best interest of the patient.
- Receipt of any additional prostate cancer specific therapy as prescribed by the treating physician.

6.0 Patient Evaluations

Pre-Study Treatment (to be completed within 6 weeks of study entry):

- Medical history will be recorded, along with performance status, AE assessment, concomitant medications, vital signs (temperature, blood pressure, breathing rate, and heart rate), weight and disease related symptoms.

- Physical exam, CBC with differential and platelets, serum chemistries (sodium, potassium, chloride, carbon dioxide, magnesium, glucose, calcium, phosphorus, BUN, albumin, total protein, bone specific and total alkaline phosphatase, creatinine, ALT and/or AST, total bilirubin, direct bilirubin, LDH, Lipase, TSH, free T4), testosterone, PSA, PT/PTT, urinalysis and urine for UPCR (24 hr urine for total protein if UPCR is >1) and N- telopeptides, radiographic studies (Bone Scan, CT scan of the Chest/Abdomen/Pelvis – PET/CT or MRI scans are also acceptable), Electrocardiogram (ECG) and specimens for correlative studies (see Section 6.1).

On-Study Treatment (evaluations have a standing window of allowance of +/- 3 days):

- **Weeks 1 through 12**: Patients will be evaluated every 3 weeks after the start of Week 1 until the end of Week 12 (ie, end of Week 3, end of Week 6, end of Week 9, and end of Week 12). Evaluations will include physical exam, vital signs, weight, toxicity review, concomitant medications, CBC with differential and platelets, serum chemistries (sodium, potassium, chloride, carbon dioxide, magnesium, glucose, calcium, phosphorus, BUN, albumin, total protein, total alkaline phosphatase, creatinine, ALT and/or AST, total bilirubin, direct bilirubin, LDH), and optional specimens for correlative studies (see Section 6.1). Imaging studies will be repeated at Week 12. If there was no evidence for soft tissue disease in the thorax at baseline, repeat CT scans of the chest may be omitted at the discretion of the treating physician. Adverse events will be recorded at each visit.

  - Patients on therapeutic Coumadin will have PT/PTT testing every week for the first 3 weeks.

  - TSH, free T4, and Lipase will be measured every 3 weeks up to and including Week

12. If no abnormalities are detected by Week 12, measurements may be repeated every 12 weeks. If abnormalities are detected, the frequency of testing will be at the discretion of the treating physician.

- PSA, bone specific alkaline phosphatase (BSAP), urinalysis and urine for n-telopeptides will be measured every 6 weeks. UPCR will be performed only if urinalysis reveals >100 mg/dL.

- **After Week 12 until completion of study treatment**: Patients treated beyond week 12 will be evaluated every 6 weeks. Evaluations will include physical exam, vital signs, weight, toxicity review, concomitant medications, CBC with differential and platelets, serum chemistries (sodium, potassium, chloride, carbon dioxide, magnesium, glucose, calcium, phosphorus, BUN, albumin, total protein, total alkaline phosphatase, creatinine, ALT and/or AST, total bilirubin, direct bilirubin, LDH), and optional specimens for correlative studies (Section 6.1). Imaging studies should be repeated every 12 weeks or sooner at the discretion of the treating physician if disease progression is suspected.

  - PSA, bone specific alkaline phosphatase (BSAP), urinalysis and urine for n-telopeptides will be measured every 6 weeks. UPCR will be performed only if urinalysis reveals >100 mg/dL.

  - TSH, free T4, and Lipase will be measured every 3 weeks up to and including Week 12. If no abnormalities detected by week 12, these tests do no need to be repeated thereafter unless clinically indicated at the discretion of the treating physician. If abnormalities are detected, the frequency of repeat testing will be at the discretion of the treating physician as clinically indicated.

  - Patients who are clinically stable for at least 6 months and for whom travel to MDACC is prohibitive (e.g. patients that live out of state) may elect to forgo q6 week clinic visits and have labs drawn locally. However, these patients must return every 12 weeks when scans are performed.

  - All concomitant medications (including over-the-counter and nutritional supplements) must be recorded in the electronic medical record or source, but not the electronic database, GURU.

Post-Study treatment

- Patients will be followed for overall survival. Survival updates will take place at 6 month intervals from the off treatment date. This will consist of a phone call, e-mail or medical record review.

6.1 Correlative Studies (mandatory at baseline, optional for subsequent time points)

- For all patients who provide informed consent, venous blood will be collected for correlative studies to include multiplex analysis of cytokines, circulating tumor cells (CTCs) will collected and distributed to Dr. Amado Zurita's lab for processing and analysis. .. Samples will be collected at the following time points: baseline, Week 3, Week 6, Week 9, Week 12, every 6 weeks thereafter (for patients

treated beyond Week 12), and at the time the patient completes treatment with cabozantinib (either for disease progression, unacceptable toxicity, or patient withdrawal, or receipt of additional prostate cancer specific therapy as prescribed by the treating physician). Additional historic tissue collection will be obtained from the MD Anderson tissue bank with prior consent to LAB03-320 and PA13-0247.

- For patients with metastatic disease to the pelvis that is accessible via trans-iliac biopsy, unilateral or bilateral bone marrow biopsies/aspirates will be collected at baseline (mandatory), at Week 6 on treatment (optional), and at the time the patient completes treatment (optional) with cabozantinib (either for disease progression, unacceptable toxicity, or patient withdrawal, or receipt of additional prostate cancer specific therapy as prescribed by the treating physician). Alternatively, when tumor is not accessible via the trans-iliac approach (e.g. ischium), image guided biopsy techniques (e.g. CT-guided) of metastatic sites and biopsies of the primary tumor (if in place) may be utilized. Aspirates will assayed for multiplex analysis of cytokines, circulating tumor cells (CTCs). Cores will be analyzed for modulation of signaling via the androgen receptor, the c-Met receptor, and VEGFRs.
    - All left over samples will be stored and banked for future use, including genetic testing, in the GU Biorepository (blood and bone marrow) and the Prostate Tissue Bank (tissue).

6.2 Study Calendar

On-study tests/visits that must occur within a defined time frame will have a standing window of allowance that is equal to +/- 3 days.

	Screening	Weekly for the first 3 weeks	Every 3 Weeks (for first 12 weeks) and Every 6 weeks after[j]	Every 6 weeks	Week 6 only	Every 12 Weeks	End of Treatment	Follow- Up
Medical History	x[a]		x					
Physical examination	x[a]		x					
Height and Weight	x[a]		x					
ECOG performance status	x[a]							
Vital Signs[f]	x[a]		x					
Baseline Symptoms/Adverse Event Monitoring	x[a]		x					
Concomitant Medications	x[a]		x					
CBC with differential and platelets	x[a]		x					
Serum Chemistry[b]	x[a]		x					
Testosterone	x[a]							
PT/PTT	x[a]	x[i]						
PSA, Bone Specific Alkaline Phosphatase	x[a]			x				
Lipase	x[a]		x[c]			x[c]		
TSH, and free T4	x[a]		x[c]			x[c]		
Urinalysis, UPCR, uNTx	x[a]			x[g]				
Imaging Chest, Abd Pelvis	x[a]					x[d]		
Bone scan	x[a]					x[d]		
ECG	x[a]							
Survival Follow-up								x[e]
Blood for Correlative Studies[h]	x		x				x	
Unilateral or Bilateral BMA/BX for Correlative Studies[h]	x				x		x	

a. Within 6 weeks of registration
b. Serum chemistries consist of sodium, potassium, chloride, carbon dioxide, magnesium, glucose, calcium, phosphorus, BUN, albumin, total protein, total alkaline phosphatase, creatinine, ALT and/or AST, total & direct bilirubin, LDH
c. Repeat every 3 weeks up to and including week 12. If no abnormalities detected by week 12, these tests do no need to be repeated thereafter unless clinically indicated at the discretion of the treating physician. If abnormalities are detected, the frequency of repeat testing will be at the discretion of the treating physician as clinically indicated

d. Imaging studies will be repeated at Week 12 and every 12 weeks thereafter. If there was no evidence for soft tissue disease in the thorax at baseline, repeat CT scans of the chest may be omitted at the discretion of the treating physician.
e. Patients will be followed by phone call, medical record review, or e-mail correspondence every 6 months for survival.
f. To include temperature, blood pressure, breathing rate, and heart rate
g. UPCR will be performed only if urinalysis reveals >100 mg/dL.
h. Mandatory at baseline, optional at subsequent time points.
i. For patients on therapeutic Coumadin. This lab may be checked locally and Coumadin dosing regulated per treating physician
j. Patients who are clinically stable for at least 6 months and for whom travel to MDACC is prohibitive (e.g. patients that live out of state) may elect to forgo q6 week clinic visit and have labs drawn locally

7.0 Dose Modifications/Toxicity Management

Patients will be treated until development of castration-resistant disease progression, unacceptable toxicity, or patient withdrawal of consent.

Subjects will be monitored closely for AEs and instructed to notify their physician and/or study nurse immediately for any and all toxicities. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay, or reduction(s), in their dose in order to continue with study treatment. Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the PI or a sub-investigator, before a decision is made to modify the dose or to hold dosing temporarily.

Permissible dose reductions are outlined in Table 3. Patients who cannot tolerate 20 mg must come off study.

Table 3. Dose Reductions

Dose Level	XL 184 Dose
0	60 mg
-1	40 mg
-2	20 mg

Permissible Alterations in Dosing Schedule
As with other TKIs, it is anticipated that for some patients, the best tolerated and most effective dose will require brief interruptions (e.g. 1 to 3 days per week) in the daily dosing of cabozantinib rather than a dose reduction. These interruptions are permissible at the discretion of the treating physician and will be recorded for data monitoring, reporting, and publication.

7.1 Warnings, Precautions, and Management of Anticipated Events

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (eg, pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal

[GI] perforation and rectal/perirectal abscess. Arterial thromboembolism (transient ischemic attack [TIA], myocardial infarction [MI]) have been reported rarely.

7.1.1 Management of Adverse Events

In the absence of an unacceptable cabozantinib-related toxicity and/or clinical signs of disease progression, subjects may continue treatment at the discretion of the investigator. Subjects must be instructed to notify their physician immediately for any and all toxicities.

Guidelines for the management of AEs (i.e. dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. If study treatment of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

The reason for treatment delay and reduced dose must be recorded in the medical record. Any dose interruption and/or treatment delay of > 4 weeks will result in the removal from study treatment.

Dosing may need to be interrupted for AEs considered not related to cabozantinib if this is clinically indicated or if causality is initially uncertain. Study treatment may be resumed at the same dose (or a lower dose per investigator judgment) if the AE is determined not to be related to cabozantinib once the investigator determines that retreatment is clinically appropriate and the subject meets the protocol re-treatment criteria.

Table 4 General Approach to the Management of Study Treatment-Related Non-Hematologic Toxicities

CTCAE Version 4 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2:	
Grade 2 AEs considered related to study treatment that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2 AEs considered related to study treatment that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	• Cabozantinib dosing should be interrupted until the AE resolves to Grade ≤1. Upon resolution to baseline or Grade ≤ 1, treatment may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced.
Grade 3:	

Grade 3 AEs considered related to study treatment which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt study treatment and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, treatment may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, treatment should be restarted with a dose reduction. Note: if the investigator believes the likelihood of a reoccurrence of the same Grade 3 AE is small due to continued prophylaxis or other effective intervention, treatment may be resumed without a dose reduction and with very careful monitoring of the subject.
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator.

Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.

Table 5 General Approach to the Management of Hematologic Toxicities

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤ 1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until resolution to ≤ Grade 1, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤ 1 and temperature to ≤ 38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator.

- ANC, absolute neutrophil count; LLN, lower limit of normal
- Neutropenia: Grade 1 (LLN ≤ ANC < 1.5 x 10^9/L; Grade 2 (1 x 10^9/L ≤ ANC <1.5 x 10^9/L), Grade 3 (0.5 x 10^9/L ≤ ANC < 1 x 10^9/L), Grade 4 (ANC < 0.5 x 10^9/L).
- Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).
- Thrombocytopenia: Grade 1 (<LLN – 75 x 10^9/L); Grade 2 (<75.0 – 50.0 x 10^9/L); Grade 3 (Platelet count ≤ 50 - 25 x 10^9/L); Grade 4 (Platelet count < 25 x 10^9/L).

7.1.2 General Guidelines for Non-Hematologic and Hematologic Adverse Events

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 4 and Table 5, respectively. These guidelines are meant to be advisory and not compulsory, at the discretion of the treating physician. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Guidance for the management of fatigue, anorexia, weight loss, non-gastrointestinal fistula, osteonecrosis of the jaw, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Investigators Brochure.

7.1.3 Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

Diarrhea

Subjects should be instructed to notify their physician and/or study nurse immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide. Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. When combination therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, a dose reduction and/or dose interruption of cabozantinib should be implemented as described in Table 3. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. A dose reductions and/or dose interruption of cabozantinib may be required as described in Table 3 if antiemetic treatment and/or prophylaxis alone is not adequate.

Agents classified as having a high therapeutic index (such as 5-HT3 receptor antagonists, or NK-1 receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or dexamethasone are recommended. Caution is recommended with the use of aprepitant or fosaprepitant and nabilone as cabozantinib exposure may be affected by concomitant administration because aprepitant and

fosaprepitant are both inhibitors and inducers of CYP3A4, and nabilone is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

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

7.1.4 Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases.

Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications (Table 6):

Table 6 General Approach to the Management of Hepatobiliary Disorders

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue study treatment with weekly monitoring of liver function tests (LFTs) for at least 4 weeks.. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue study treatment with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and still Grade 1 or Grade 2	Continue study treatment with at least twice weekly monitoring of LFTs for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator.
Subjects AST or ALT > 3.0 but ≤ 5.0 x ULN at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and still Grade 2 or Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until LFTs resolve to baseline and Grade ≤ 2. Study treatment may then be resumed at a lower dose as determined by the investigator.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × ULN, total bilirubin < 1.5 × ULN, aminotransferases < 2.5 × ULN or baseline).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase [ALP]) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), as the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤ 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

7.1.5 Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week- see Tables 7 and 8). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Table 7 Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 elevations recur, then treatment must be interrupted again and till lipase and amylase levels have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.

Table 8 Symptomatic Pancreatitis

Pancreatitis	
Grade 1	Continue at current dose level. More frequent monitoring of lipase and amylase and radiographically is recommended
Grade 2	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 2 pancreatitis is at the same dose and Grade 2 pancreatitis recurs, then treatment must be interrupted again and till resolution to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced dose per investigator judgment.

7.1.6 Skin Disorders

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

The onset of PPE is variable with paresthesia (tingling, numbness) being the characteristic initial manifestation, which can be accompanied by slight redness or mild hyperkeratosis. PPE advances with symmetrical painful erythema and swollen areas (edema) 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.

Aggressive management of symptoms is recommended, including early dermatology referral (Table 9). Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo). In the case of study treatment-related skin changes (eg, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Table 9 Management of Hand-Foot Syndrome

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
No apparent toxicity	Prophylaxis with Ammonium lactate 12% cream (Amlactin®) twice daily OR heavy moisturizer (e.g. Vaseline) twice daily
Grade 1	Continue treatment at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	Reduce study treatment to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time (eg, peeling, blisters, bleeding, edema, or hyperkeratosis or affects self-care) or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was reduced, then upon resolution to Grade 0 or Grade 1, treatment may continue at the reduced dose. If the dose was only interrupted but not reduced, then treatment may be restarted at one dose level lower.

Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

7.1.7 Embolism and Thrombosis

In clinical studies with cabozantinib, venous thrombotic events (DVT and PE) have been observed in less than 10% of subjects, and arterial thromboembolic events (MI and TIA) have been reported rarely. In addition, subjects with cancer have a significantly increased likelihood of developing thromboembolic complications.

Subjects who develop a PE and/or DVT should have study treatment interrupted until full anticoagulation is established with low molecular weight heparin (LMWH) or Coumadin. Anticoagulation with LMWH is preferred over Coumadin if possible and feasible. Venous filters (e.g. vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

7.1.8 Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold 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. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking new therapeutic action. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained $\geq$ 160 mm Hg systolic or $\geq$ 110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (Table 10).

Table 10 Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of cabozantinib • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. • Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.

BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure

NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria

7.1.9 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Development and worsening of proteinuria should be monitored by serial urinalysis (qualitative/semiquantitative assessment by dipstick; quantitative assessment by urine protein/urine creatinine ratio [UPCR], or 24-hour urine protein excretion). When a UPCR exceeds 1 (mg/dL protein / mg/dL creatinine), a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. 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) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in Table 11.

Table 11 Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• Confirm with a 24 hour urine protein excretion within 7 days • If proteinuria of > 1 g/24 hours is confirmed, hold cabozantinib and continue with UPCR monitoring. When UPCR returns to < 1, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

7.1.10 Hemorrhage

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

- Tumor lesions of the lung with cavitations or tumor lesions which invade, encase, or abut any major blood vessels; non-small cell lung cancer (NSCLC) with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. The anatomic location and characteristics of tumor as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.

- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis

Based on the described predisposing risk factors for hemoptysis, many studies with antiangiogenic drugs exclude subjects with NSCLC and squamous cell differentiation. Although enrollment of subjects with NSCLC with squamous cell differentiation has been allowed on cabozantinib studies, cabozantinib studies exclude NSCLC subjects with any of the following: tumors abutting, encasing, or invading a major blood vessel; cavitating lesions; history of clinically significant hemoptysis; or recent (within 3 months) radiation therapy to the thoracic cavity including brachytherapy unless radiation therapy targets bone metastasis.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis ($\geq$ 0.5 teaspoon (2.5ml) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

7.1.11 Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

7.1.12 Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula:

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

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

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with such agents (eg, bevacizumab). Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 3 months of starting treatment with cabozantinib. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

7.1.13 Wound healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half lives) prior to elective surgery.

7.1.14 Endocrine Disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects. In Study XL184-203, 17 of 34 (50%) euthyroid subjects with castration-resistant prostate cancer (CRPC) developed abnormal thyroid-stimulating hormone (TSH) levels 6 weeks after initiation of cabozantinib treatment (6% showed TSH levels between 5 and 7 mU/L, 44% had TSH > 7 mU/L). The median TSH level at week 6 was 5.2 mU/L (range, 0.02-29.7 mU/L). In a Phase 1 combination study of rosiglitazone and cabozantinib (XL184-008) to determine the potential for a clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are enrolled. Among 11 evaluable subjects, the AE of hypothyroidism was reported in 55% of subjects. Currently available data are insufficient to determine the cause of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is recommended. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

7.1.15 Guidelines for Prevention of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Three cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of IB. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of

study treatment must be discussed with and approved by the Sponsor on a case by case basis.

7.2 Potential Drug Interactions

Cytochrome P450: Preliminary 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 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 (but not a CYP2C9 or CYP2D6 substrate), based on data from in vitro studies using CYP-isozyme specific neutralizing antibodies. Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, 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. In addition, 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.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% 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, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors 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.

Because in vitro studies only assessed the metabolizing capacity of the CYP3A4, CYP2C9, and CYP2D6 pathways, the potential for drugs that inhibit/induce other CYP450 pathways (eg, CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.

As warfarin is metabolized through the CYP450 system, therapeutic anticoagulation with warfarin (eg, Coumadin) is not recommended. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (eg, Lovenox) or heparin. However, Cabozantinib undergoes only minor CYP2C9 metabolism and does not inhibit CYP2C9. Thus, there is no specific drug-drug contraindication and Coumadin can be utilized in select patients if LMWH is not feasible.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007; *http://medicine.iupui.edu/clinpharm/ddis/table.aspx*).

Protein Binding: Cabozantinib is highly protein bound (approximately 99.9%) 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). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions: In a relative bioavailability study in dogs cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors (PPIs) and H_2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs and H_2-antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of PPIs (eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (eg, ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H_2 blockers is preferred over PPIs (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib). Antacids, H_2 blockers, or PPIs should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity. Additional details related to these overall conclusions are provided in the Investigators Brochure.

8.0 CRITERIA FOR SAFETY AND EFFICACY EVALUATION

8.1 Safety Evaluation

All patients who receive at least one dose of cabozantinib will be evaluated for safety parameters. Additionally, any occurrence of a SAE from time of consent forward up to and including follow-up visits will be reported. Safety will be evaluated for all treated patients using the NCI CTCAE version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations and clinical laboratory tests.

8.2 Efficacy Evaluation

All patients who receive at least one month of cabozantinib will be considered evaluable for efficacy. The PI will complete evaluation of bone scans and RECIST tumor measurements (if applicable) and document them on standard MDACC forms in the medical record.

9.0 Statistical Methods

Objectives and Sample Size: This is a phase II study of cabozantinib in patients with previously untreated androgen-dependent disease. The primary objective is to assess progression-free survival (PFS). We will assess response and overall survival as secondary endpoints. A maximum of 60 patients will be entered into this trial, at an expected accrual rate of 2-3 patients per month. The trial will require approximately 24 months for patient accrual and an additional 9 months for patient follow-up. If the trial continues to maximum accrual and maintains sufficient follow-up to observe 49 progression events with a median PFS of 11.2 months, then a 95% credible interval for median PFS would extend from 8.5 to 14.9 months. Based on historical mean survival time 11.2 months, a mean progression-free survival time on average > 13 months would be considered promising evidence of anti- disease activity.

Design and Interim Analysis: This is phase II study and a Bayesian model will be used to monitor the trial with a recommendation to stop the trial if the PFS is worse than historical data. In particular, we assume that time to progression T follows an exponential distribution with mean μ and $\mu^* = \text{median}(T) = \mu\log(2)$. The trial will be stopped if $\Pr(\mu^* < \mu_H^* \mid \text{data}) > 0.95$, where μ_H^* is the median PFS with an inverse gamma distribution IG(22.07, 235.99), which corresponds to a 95%CI of (7.3, 17.0) based on the historical data (Millikan, et al., 2008). The prior for μ^* is assumed to be IG(a, b), where the parameters a =3.25 and b = 25.25 is determined based on PFS with the same mean (11.2 months) and a larger standard deviation of 10. Assuming an accrual rate of 2.5 per month, the operating characteristics for the futility stopping rule under various true states are summarized in the following table, with results based on 1000 simulations.

Median PFS	Prob(Stop Early)	Mean No. of Patients (25%, 75%)
13.2 months	0.019	59.2 (60, 60)
11.2 months	0.072	57.4 (60, 60)
9.2 months	0.246	52.2 (60, 60)
7.2 months	0.700	40.5 (24, 60)
6.2 months	0.924	31.2 (17, 44)

A Bayesian sequential monitoring method (Thall, 1995) will be used to monitor for any study treatment related Grade 4 toxicity that fails to resolve to <Grade 2 within 14 days after the cabozantinib is held.

We stop the trial if the toxicity is likely to be greater than 30%. That is, stop the trial if

$$\text{Prob}\{\text{toxicity rate} > 30\% \mid \text{data}\} > 0.85.$$

The prior distribution of toxicity rate is assumed to be beta (1, 1). Following this rule, the trial will be terminated due to toxicity if [# toxicity]/[# patients evaluated] ≥ 5/10, 9/20, 12/30, 15/40, 19/50, or 22/60. The operating characteristics table is given in the following table, based on 1000 simulations:

true Prob(tox)	Pr(stop)	mean # Pts (median)
0.1	0.001	59.9 (60)
0.2	0.04	58.0 (60)
0.3	0.32	47.7 (60)
0.4	0.79	29.2 (20)
0.5	0.98	16.9 (10)

The trial will be conducted through the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is hosted on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to personnel responsible for enrolling patients and reviewing and analyzing patient data. Training on the use of the Clinical Trial Conduct website will be provided by the study statistician for study personnel prior to the study initiation.

Demographic and baseline laboratory results will be summarized using descriptive statistics, including means with standard deviations, or medians with ranges, histograms and box-plot. Survival or times to failure and time-to-progression functions will be estimated using the Kaplan-Meier method. Failure will be classified as: Death due to prostate cancer or unknown cause; disease progression, need for palliative radiation to more than 1 site, or serious adverse event deemed related to study agent. Toxicity will be reported by type, frequency and severity. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements.

10.0 DATA AND PROTOCOL MANAGEMENT

10.1 Registration Procedure and Data Reporting

All data will be entered to the Department of Genitourinary Medical Oncology Oracle database (GURU). GURU is a password protected database with an audit trail. Data can be collated with a unique GURU identification in order to de-link information. The minimum required fields will be entered to the MDACC required data collection systems (CORe/PDMS). Registration data entry will occur prior to initiation of therapy. All eligibility criteria must be satisfied. Reporting to the supporting agency will follow the contract agreement.

10.2 Clinical Trial Posting

Information related to this study will be posted on www.clinicaltrials.gov before the first patient is enrolled in the study.

11.0 SAFETY AND ADVERSE EVENT REPORTING

11.1 Reporting Requirements

11.1.1 Adverse Drug Reaction Reporting

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Adverse events will for this protocol will be documented and entered into the case report form according the Recommended Adverse event Recording Guidelines for Phase II protocol.

Table 12.

Recommended Adverse Event Recording Guidelines					
Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I	Phase I	Phase I	Phase I	Phase I

	Phase II	Phase II Phase III	Phase II Phase III		Phase II Phase III	Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

11.1.2 **Serious Adverse Event Reporting (SAE)**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this should be documented to the extent that information is available.

- This report must be submitted by the study site to Exelixis or designee within one to two business days, even if it is not felt to be drug related. Email: drugsafety@exelixis.com; Fax 650-837-7392
- The investigator agrees to provide supplementary information requested by the Exelixis Drug Safety personnel or designee.
- Pregnancy, although not itself an SAE, should also be reported on an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Regulatory Reporting:

All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to the Food and Drug Administration (FDA) by the investigator as required by 21 CFR 312.32.

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or the MDACC SAE form.

  The final MedWatch or MDACC Form must be submitted by the study site to

Exelixis within one to two business days of submission to the FDA to allow Exelixis time to cross-report to Exelixis' IND. Email: drugsafety@exelixis.com; Fax 650-837-7392

11.2 Clinical Laboratory Adverse Events

The results of all laboratory tests required by the protocol will be recorded in the patient's medical record. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the diagnosis that explains them is made.

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a SAE, and/or
5. Test result is considered to be an adverse event by the investigator.

*Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet Condition 2 above for reporting as an adverse event.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for Condition 4.

11.3 Management of Persistent and Refractory Toxicity

Utilizing the NCI CTCAE (version 4.0), events which are moderate and interfere with function that are not consistent with a patient's medical history, and are refractory to medical treatment, should be investigated carefully to ensure that no other etiology is present. Study drug will be held for any toxicity events deemed definitely, probably, or possibly drug-related (such as diarrhea, hypertension, vomiting, diarrhea, and dizziness) and that are greater than grade 2. Drug will be held until severity is reduced to Grade 1 or less and then resumed daily dosing with a dose reduction as outlined in Section 6.0.

11.4 Management of All Other Toxicities

Other toxicities may occur. Supportive care should be prescribed as needed. They may also be prescribed prophylactically to prevent toxicity from developing or

recurring. The examples include anti-emetics for nausea/vomiting, analgesics for pain, antipyretics for fever and antidiarrheals for diarrhea

Abnormal laboratory values will be only be captured as adverse events if they are Grade 3 or higher.

11.5 Other Safety Considerations

11.5.1 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 (eg, 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.

11.5.2 Medication Errors/ Overdose

Any study drug administration error or overdose that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis or designee.

11.5.3 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 last dose of 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 ***> 30 days after the last dose*** of study treatment. The status of all other continuing AEs will be documented as of 30 days after the last dose of study treatment.

12.0 PUBLICATION 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 prior to submission and also comply with any provisions regarding publication as are agreed to between the PI's institution (eg, institution name.) 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 according to guidelines established by the International Committee of Medical Journal Editors.

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