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Title: A Phase II Study of Cabozantinib (XL184) in Patients with Advanced/Metastatic Urothelial Carcinoma

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* not responsible for patient care

Roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
F. *Studying, interpreting, or analyzing coded, linked data or specimens for research purposes*
G. *Some/all research activities performed outside NIH*

CTEP Supplied Agents:

Drug Name:	Cabozantinib (XL184)
IND Number:	116059
NSC Number:	761968
Sponsor:	CTEP
Manufacturer:	Exelixis

Commercially available agents:

^{18}FDG and Na^{18}F will be supplied from commercial sources by the NCI Molecular Imaging Program

PRÉCIS

Background:

- In the United States, urothelial carcinoma (UC) of the bladder is the fourth most common malignancy in men and the ninth most common in women with an estimated 69,250 new cases and 14,990 deaths in the year 2011
- There is no FDA-approved second line drug for patients with metastatic UC
- Multiple lines of evidence support targeting angiogenesis in UC
- In human bladder cancer, overexpression of c-Met/Axl/PDGFR-α or c-Met alone showed significant correlation with poor survival
- Cabozantinib is a new chemical entity that inhibits multiple receptor tyrosine kinases with growth-promoting and angiogenic properties.
- The primary targets of cabozantinib are MET, VEGFR2, and RET

Objectives:

- To determine the response rate of cabozantinib in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy

Eligibility:

- Patients in cohort 1 must have a histologically confirmed diagnosis of metastatic, progressive urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis.
- Patients in cohort 2 must have a histologically confirmed diagnosis of bone only metastatic, urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis.
- Patients in cohort 3 must have a histologically confirmed diagnosis of non-transitional cell carcinoma cancer (including but not limited to squamous cell, neuroendocrine, adenocarcinoma including urachal and sarcomatoid) of the bladder, urethra, ureter, or renal pelvis.
- Patients must have been previously treated, as defined by treatment with <u>at least</u> one prior cytotoxic chemotherapy regimen or agent. Patients may have received any number of prior cytotoxic agents.
- 18 years of age or older.

Design:

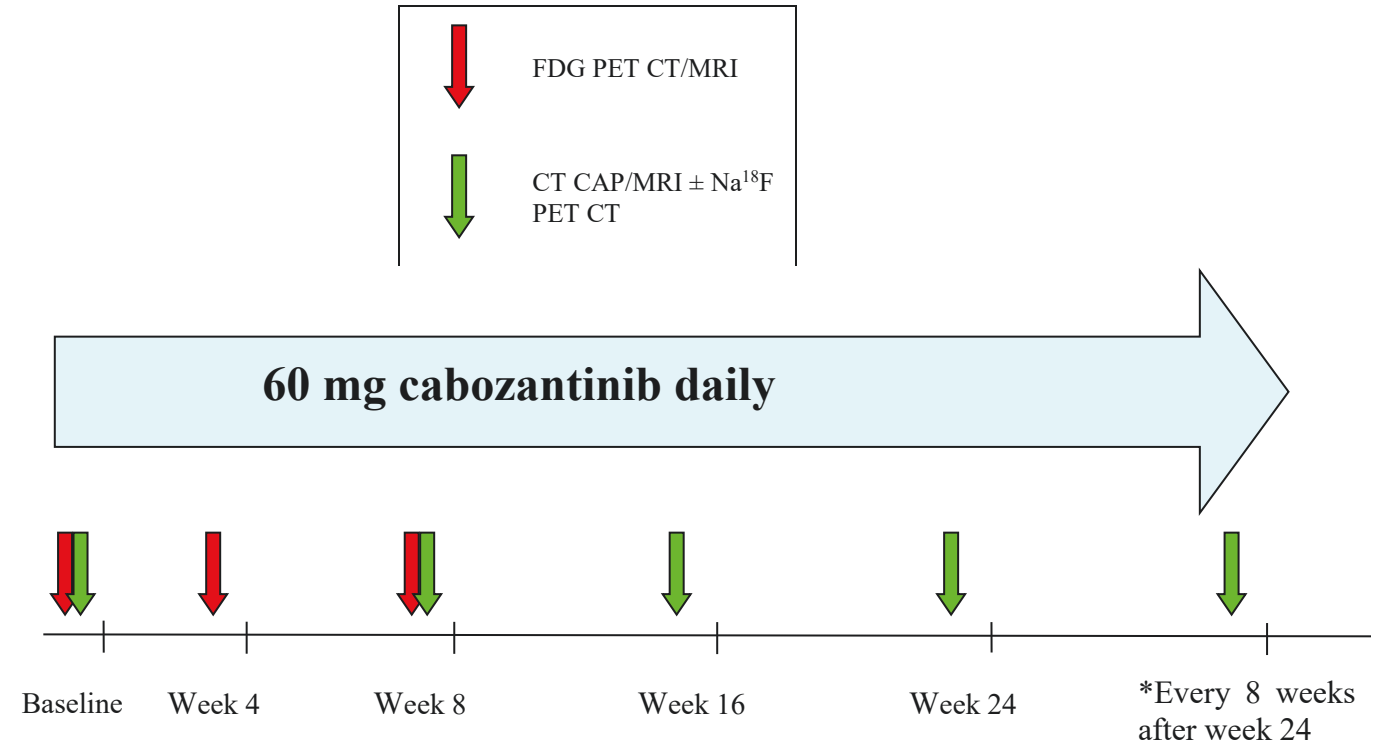
- A maximum of 71 subjects will be enrolled in this open label, non-randomized, phase II trial of 60 mg each day of cabozantinib. Up to 50 patients will be accrued to cohort 1 (metastatic, progressive urothelial cancer). The remainder will be enrolled on exploratory cohorts 2 & 3, bone only metastatic urothelial disease and non TCC bladder cancer respectively, during the time the study is accruing patients for cohort 1. Note: Patients who tolerate cabozantinib at 60 mg daily during the first 2 cycles (first restaging time period) without ≥ grade 2 toxicity may undergo dose escalation to 80 mg daily at the discretion of the Principal Investigator.
- A Simon 2 stage design with alpha=0.05 and beta = 0.10 as acceptable error probabilities. Initially 21 subjects will be enrolled and followed for progression. If 2 or more of cohort 1 subjects experiences a response, enrollment will continue until a total of 41 evaluable

subjects with progressive urothelial cancer have been entered. 2-3 patients per month may enroll on this trial; thus, 2 to 3 years is anticipated as the accrual period.

- Each patient will undergo response evaluation assessments with CAP CT (or MRI) with or without $Na^{18}F$ PET CT every 8 weeks while on active protocol therapy starting at baseline. Patients will undergo investigational FDG PET/CT and PET/MRI (optional) at baseline, week 4 and week 8.

SCHEMA

TREATMENT AND IMAGING SCHEDULE



* Every 12 weeks for patients on drug holiday.

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1 OBJECTIVES

1.1 PRIMARY OBJECTIVE

- To determine the response rate of cabozantinib in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy.

1.2 SECONDARY OBJECTIVES

- To measure the PFS of cabozantinib as determined by RECIST (version 1.1).
- To determine the safety and toxicity of cabozantinib in this previously treated patient population.
- To estimate overall survival of patients with metastatic urothelial carcinoma of the bladder treated with cabozantinib.
- To explore the relationship between the biodistribution changes in FDG PET/CT parameters and the clinical response.
- To assess RECIST criteria semi-automated volume (SAV), SACT, MASS criteria and Choi criteria in metastatic target lesions.
- To compare the change in Hounsfield units (HU) with the SUV change with treatment response in metastatic lesions.
- To perform correlative studies assessing potential biomarkers of response to XL184.

1.3 EXPLORATORY OBJECTIVES

- To perform exploratory evaluation of response criteria in urothelial cancer patients who have not progressed by RECIST, but have developed bone lesions.
- To perform exploratory evaluation of response criteria in patients with non-transitional cell carcinoma of the bladder.
- To conduct preliminary studies in genetic changes in tumor vs. normal tissue in order to begin to identify specific genetic or chromosomal changes that lead to cancer.
- To assess quality of life in patients treated with cabozantinib.

2 BACKGROUND

2.1 UROTHELIAL CANCER

In the United States, urothelial carcinoma (UC) of the bladder is the fourth most common malignancy in men and the ninth most common in women with an estimated 69,250 new cases and 14,990 deaths in the year 2011.[1] Worldwide, 386,300 new cases and 150,200 deaths occurred from bladder cancer in 2008[1]. Although UC is a chemosensitive malignancy with response proportions of over 50% with conventional cytotoxic regimens, the response durations are short and the median survival of patients with metastatic disease is approximately 14 months[2]. There is no FDA-approved second line drug for patients with metastatic UC and no standard conventional chemotherapy agent(s) have demonstrated a survival benefit in patients that have progressed after first line platinum-based chemotherapy. Second-line trials with cytotoxic agents have generally yielded discouraging response rates (see **Table 1** below) with a median progression-free survival between 2 to 3 months and a median survival in the range of 6 to 9 months[3-6]. Furthermore, many patients receive these agents as part of first-line therapy leaving few available options for patients

with progressive or recurrent disease. This highlights the need for the development of novel therapies for the treatment of patients with metastatic UC.

Table 1. Results with cytotoxic agents in patients with metastatic urothelial carcinoma who had received prior chemotherapy

Agent	Activity	
	Overall Response	95% CI
Paclitaxel[4,7,8]	9-10%	0-17%
Docetaxel[3,9]	13%	4-30%
Ifosfamide[10-12]	20%	10-32%
Gemcitabine[13,14]	23%	8-38%

Targeting Angiogenesis in UC

Several processes central to tumor progression, including tumor growth, invasion, and metastasis are dependent on an adequate blood supply. Angiogenesis, the process by which the neovascular blood supply is recruited, is orchestrated by a balance of stimulatory and inhibitory factors released by tumor and host cells. Over twenty years ago, Chodak et al first demonstrated that the urine of patients with UC contained pro-angiogenic substances [15]. Multiple lines of evidence support targeting angiogenesis in UC:

- Microvessel density, a histological measure of angiogenesis, has been correlated with stage, recurrence, and survival, in UC. [16,17], [18]
- Several reports have described increased expression of vascular endothelial growth factor (VEGF), a mediator of angiogenesis, in the tissue, serum, and urine of patients with UC and correlated these markers with stage and prognosis.[19-21]
- Inhibitors of angiogenesis have shown activity in preclinical murine models of UC.[22-24]
- A functional autocrine loop involving VEGF/VEGFR2 may be important in the pathogenesis of some bladder cancers. In a recent non-clinical study, 6 of 13 bladder tumor cell lines examined expressed VEGFR2 (Flk-1). Further analysis of the T24 bladder tumor cell line revealed a functional autocrine loop involving VEGF and VEGFR2.[25,26]

Clinical studies in bladder cancer with anti-angiogenic agents.

A phase II study of single agent Sunitinib [27] in 77 patients on one of two schedules (50 mg per day for 4 weeks on and 2 weeks off [cohort A], 37.5 mg per day continuously [cohort B]), found a partial response in three of 45 patients in cohort A, and in one of 32 patients in cohort B. Clinical regression or stable disease was achieved in 33 of 77 patients (43%) with 29% of patients achieving stable disease lasting longer than 3 months. Antitumor responses were observed, identifying the vascular endothelial growth factor axis as a viable pathway for UC treatment.

A phase II study of 43 metastatic or unresectable chemo naïve UC patients treated with cisplatin, gemcitabine, and bevacizumab as first-line chemotherapy reported complete response 19%, partial response 53%; with overall response rate of 72%. Stable disease lasting greater than 12 weeks was

observed in 9%. With a median follow-up of 27.2 months (range, 3.5 to 40.9 months), median progression-free survival (PFS) was 8.2 months (95% CI, 6.8 to 10.3 months) with a median overall survival (OS) time of 19.1 months (95% CI, 12.4 to 22.7 months). This combination demonstrates significant clinical activity in the first-line treatment of metastatic UC patients. A phase III trial to further define the toxicity risk vs. clinical benefit of bevacizumab addition to platinum-based doublets is currently ongoing in this population.

Met expression in Bladder Cancer

The c-met proto-oncogene encodes a receptor tyrosine kinase (Met) and has been shown to play a role in oncogenesis. High titers of hepatocyte growth factor, the specific ligand for Met, are excreted in the urine and tend to reflect disease activity of bladder cancer. The clinical significance of Met in human bladder cancer was examined in bladder cancer cell lines and human bladder cancer tumors. The mRNA expression and genomic alteration of c-met was studied in five bladder cancer cell lines. Met overexpression was then compared with p53 nuclear accumulation (TP53) in primary bladder cancer (n = 142 patients). Expression of c-met tended to correlate with differentiation of cancer cell lines in the absence of point mutations. Expression of Met was positively associated with histologic grade, stage classification, tumor size, and nodular tumor growth (P <.05, respectively). Indicators for poor long-term survival were invasive cancer, multiple tumors, and Met overexpression (P =.0006, .01, and.04, respectively). In these studies, the c-met proto-oncogene demonstrated that it plays an important role in the progression of bladder carcinogenesis[28].

The clinical significance of the expression of phosphorylated c-Met in bladder cancer, and its correlation with cancer cell progression-related molecules has also been investigated by Miyata et al.[29]. The expression levels of 2 tyrosine residues of c-Met (pY1234/1235 and pY1349) were examined immunohistochemically (IHC) in 133 specimens with non-metastatic bladder cancer and their correlation with matrix metalloproteinase–1, –2, –7, and –14; urokinase-type plasminogen activator; E-cadherin; CD44 standard, variant 3, and variant 6; and vascular endothelial growth factor. Expression of phosphorylated c-Met was detected in cancer cells, but was rare in normal urothelial cells. c-Met, pY1349 was associated with high pathologic T stage in a multivariate analysis. Expression of pY1349 c-Met was a marker of metastasis and (P = .001) and cause-specific survival (P = .003). Expressions of matrix metalloproteinase–2, matrix metalloproteinase–7, and E-cadherin correlated with pY1349 c-Met expression. This demonstrates that pY1349 c-Met plays an important role in tumor development, and its expression is a significant predictor of metastasis and survival of patients with bladder cancer.

A study using antibody arrays that selected antibodies against targets differentially expressed in bladder tumors, found serum protein, c-met, to be top ranked at identifying bladder cancer patients from controls[30]. C-met expression was validated by immunohistochemistry of tissue microarrays containing bladder tumors (n = 173) and was associated with pathological stage and tumor grade (p<0.001), and over-all survival (P=0.044).

NIH-Met5 and T24-Met3 cell lines harboring an inducible human c-Met gene were established. C-Met-related receptor tyrosine kinases were screened by microarray analysis. The potential clinical importance was examined in a cohort of 65 cases of locally advanced and metastatic bladder cancer patients. A positive association of Axl or platelet-derived growth factor receptor-alpha (PDGFR-α) with c-Met expression was demonstrated at translational level, and confirmed by specific siRNA knock-down. The transactivation of c-Met on Axl or PDGFR-α in vitro was

through a ras- and Src-independent activation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) pathway. In human bladder cancer, co-expression of these receptor tyrosine kinases was associated with poor patient survival ($p < 0.05$), and overexpression of c-Met/Axl/PDGFR-α or c-Met alone showed the most significant correlation with poor survival ($p < 0.01$)[31].

C-Met Inhibitor in Bladder Cancer Cell Lines

Met overexpression occurs in bladder cancer[28,29,31,32]. The effects of a small, orally available, highly selective Met tyrosine kinase inhibitor, PF-2341066, was studied in a pre-clinical model of bladder cancer. Bladder cancer cell lines (HT 1376, T24 and TCC-sup) were treated with PF-2341066 to determine its effects on cellular proliferation and migration. Migration was inhibited in a dose dependent manner when the cells were treated with PF-2341066 (Bottaro, NCI, UOB, unpublished).

Dual Targeting VEGF and C-MET

Hypoxia has been shown to result in the upregulation of both MET and VEGF, and activated MET can indirectly promote angiogenesis and tumor growth by upregulating VEGF expression [33],[34]. Evidence from the literature [34] also supports cooperative roles for MET and VEGFR2 in the proliferation and survival of the tumor endothelium. Thus, simultaneous inhibition of both MET and VEGFR2 should result in near-complete inhibition of major survival pathways that are induced in tumors by hypoxia.

2.2 IND AGENT - CABOZANTINIB (XL184)

XL184 (cabozantinib) inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2011). The primary targets of XL184 are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in *vivo* pharmacodynamic activity of XL184 against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

RTKs regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair[35]. Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand has been implicated as causative factors in the development and progression of numerous human cancers.

The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF)[35]. c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's Brochure, 2011). c-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3)

genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorigenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (e.g., NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo[35].

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity[36], either by means of c-Met kinase overexpression[37], activating c-Met gene mutations and/or amplification[37-39], or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF. These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis[40].

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability[41]. Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer[42]. High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer and poor survival.

Nonclinical Development of XL184

In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors[43]. In RIP-Tag2 transgenic mice, tumors treated with XL184 were smaller (P <0.05) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive (P <0.05) and had no liver metastases [44]. All mice treated with XL184 (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days [45]. Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg [46]. XL184 increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, XL184 disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors (P <0.001) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses (P <0.01), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, XL184 inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all

doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of XL184 was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone[47]. ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 or vehicle daily (qd) for 7 weeks of treatment[48]. Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 treated animals appeared mostly normal. Thus, XL184 treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of XL184 and at plasma exposures comparable to exposure observed in clinical trials[49]. XL184 produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of XL184. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of XL184 resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg[49]. Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met [46]. This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy[49]. In rats, plasma concentrations in the range of 5 to 15 μM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 μM were observed at highly efficacious doses in mice. These results were consistent with *in vivo* target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats[49]. In rats, the oral bioavailability of XL184 dosed as a solid was approximately 100% of XL184 dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single XL184 oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) [49]. With repeat daily oral dosing in rats, systemic exposure (AUC_{0-t} values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The C_{max} and AUC_{0-t} values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to XL184 in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (C_{max} and AUC_{0-t} values) associated with single XL184 oral doses in dogs increased less than dose-proportionally with increasing XL184 dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption [48]. With repeat daily dosing, exposure (C_{max} and AUC_{0-24} values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

Toxicology

In rodents and non-rodents, histopathological changes associated with XL184 administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues [48]. Histopathological changes present in the bone and pancreas were considered secondary to XL184 administration. Adverse effects following oral exposure to XL184 were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, XL184 administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg XL184 capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study[49]. In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184-treated rats or on cardiovascular function in XL184-treated dogs.

Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with XL184 treatment 1) as a single agent at does ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure[48]. Safety and efficacy information, from the 2011 Investigator's Brochure, is summarized below.

Phase I Studies

Study **XL184-001** was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) to 265 qd (using capsules [25 and/or 100mg] for two, 14-day cycles) were enrolled. The capsule MTD was determined to be 175 mg qd[50]. Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease enrolled in the dose expansion phase, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of ≥30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

In Study **XL184-002**, treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2011 Investigator's Brochure. All adverse events (AEs) were assessed with respect to combination treatment and not the individual components. Nineteen patients were evaluated for AEs, the most common grade 3 or higher included neutropenia (21%), thrombocytopenia (16%), leucopenia (16%), and hypertension (11%). Myelosuppression, including prolonged pancytopenia, is a dose-limiting toxicity (DLTs) associated with TMZ use. The frequency at which bone marrow toxicity was observed in this study is consistent with the TMZ prescribing information.

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. See "Pharmacokinetics" section for results.

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. See "Pharmacokinetics" section for results.

In Study **XL184-008**, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients

evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase 1 study, **CA205-001**, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. Because of a change in study sponsor, this study was reinitiated as **XL184-014.** One additional subject was enrolled as of May 2011 at 50 mg PO qd.

Study **XL184-202** was a phase 1b/2 trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase 1 dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A cPR was observed in 5 subjects (8%) and 24 subjects (37%) had SD/PR ≥4 months. The most common grade 3 or higher AEs in the phase 1 portion included diarrhea (44%), fatigue (22%), hypokalemia (11%), decreased appetite (6%), dyspnea (14%), lipase increase (6%), hypomagnesemia (6%), and dehydration (5%). Twenty-eight subjects were enrolled in the phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced progressive disease (PD), received single-agent cabozantinib or cabozantinib with erlotinib. AEs ≥grade 3 included dehydration (8%) and hypertension (8%). One patient, who was treated with single-agent cabozantinib, had a cPR.

Phase 2 Studies

In a phase 2 study, **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal rSAEs.

Study **XL184-203** is a phase 2 randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal SAEs.

Study **XL184-205** is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3), and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one

grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Adverse Events

The clinical studies with XL184 are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with XL184 (806 in single-agent studies and 107 in combination studies of XL184 with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2011). Data from the 806 subjects who received single-agent XL184 show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination XL184 studies. The most commonly reported SAEs that were assessed as related to study treatment with XL184 (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

Grade 5 AE data are available for 1404 subjects who have been dosed with cabozantinib as a single agent (1286) or in combination (118) through June 1, 2012. There have been 27 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), pulmonary hemorrhage (one subject), esophageal hemorrhage (one subject), PE (two subjects), respiratory failure (three subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (four subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), tracheo-esophageal fistula (one subject), esophageal fistula (one subject), hemorrhage (two subjects), hepatic failure (one subject), bronchopneumonia (one subject) cardiac arrest (one subject), sepsis (one subject), and diverticular perforation, peritonitis (one subject) (Exelixis Communication). The initial daily doses of drug in these subjects were 100 mg (8 subjects), 125 mg (8 subjects), 175 mg (11 subjects). In 2 subjects, the initial dose of 125 mg was reduced to 50 and 75 mg respectively prior to death.

Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial **XL184-001** showed dose proportional increases in maximum plasma concentration (C_{max}) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg) (Kurzrock, 2011). Terminal-phase half-life ($t_{1/2,z}$) values were 59.1 to 136 hours (Investigator's Brochure, 2011). After repeat dosing, $t_{1/2,z}$ values (mean ± standard deviation) for XL184 were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by Day 15 (Kurzrock, 2011). Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Patients who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 (7.68 ± 2.85 mcg·h/mL; n = 23 vs. 41.6 ± 15.3 mcg·h/mL; n = 23), indicating that XL184 accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal $t_{1/2,z}$ of cabozantinib appeared to

be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). 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 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.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, 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 must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

2.3 RATIONALE

2.3.1 Rationale for cabozantinib in UC

Bladder cancer is a highly vascular malignancy that produces high levels of pro-angiogenic factors including VEGF, bFGF and IL-8. Microvessel density, a histological measure of angiogenesis, has been correlated with stage, recurrence, and survival in this disease. Clinical studies in bladder cancer with anti-VEGF pathway agents have shown anti-tumor activity. While these studies validate the potential for an anti-angiogenic approach to UC, they also indicate the need to investigate alternative ways to target the tumor vasculature. Of particular interest are agents that target more than one mechanism for tumor growth and development and have activity in tumors resistant to existing therapies. Cabozantinib is an oral, potent inhibitor of MET and VEGFR2 that produces robust antiangiogenic, antiproliferative, and antiinvasive effects in preclinical models. MET and VEGFR2 are key mediators of angiogenesis. Preliminary results of randomized phase II studies with cabozantinib in CRPC and ovarian cancer have demonstrated clinical activity. MET activation is common in solid tumors including UC and promotes proliferation, invasion, and metastasis. For these reasons, co-targeting of the MET and VEGF signaling pathways using cabozantinib may represent a promising treatment strategy.

2.3.2 Rationale for a PFS Endpoint

Pertinent to the issue of discovering new drugs active in urothelial cancers is that identifying clinical benefit should not be limited to response. Some of the newer "targeted therapy" agents approved by the FDA have been approved on the basis of improved progression-free survival (PFS) and not response rate (e.g., sorafenib in renal cell carcinoma with a response rate of approximately 10% but a major impact in PFS and, eventually, an improvement in survival). This

being said, the median progression-free survival for bladder cancer patients treated with chemotherapy is modest at only 2-3 months and response rates are in the 10-20% range. In a second-line trial of weekly paclitaxel in 31 patients with progressive urothelial cancer, the median time to progression was 2.2 months[4]. In an ECOG trial evaluating the epothilone analog BMS-247550 in patients with relapsed urothelial cancer, the median progression-free survival was 2.7 months (95% CI, 1.8, 4.1)[5]. In a phase 3 randomized second-line trial of vinflunine versus best supportive care, the PFS for patients treated with vinflunine was 3.0 months (95% CI, 2.1, 4.0)[51]. Novel therapies are desperately needed for these patients and identifying activity in the refractory setting by using PFS is considered an acceptable approach with these new targeted agents.

2.3.3 Rationale for Cabozantinib Dose Selection

A cabozantinib starting dose of 100 mg qd has been studied in 171 CRPC subjects enrolled to the Phase 2 XL184-203 RDT. Despite relatively high rates of cabozantinib dose reductions to the next lowest dose of 60 mg qd within the first 12 weeks of therapy (51%), this starting dose resulted in high rates of pain relief, bone scan improvement, and overall disease control.

Preliminary data from a separate and ongoing dose-ranging study looking at lower doses of cabozantinib in CRPC coupled with results from a retrospective review of the Phase 2 XL184-203 RDT indicate that lower doses below 100 mg qd are likely to retain efficacy while improving upon tolerability:

Preliminary results from an ongoing dose-ranging study: To date, 9 subjects with metastatic CRPC enrolled to the first cohort (starting dose of 40 mg qd) are evaluable for bone scan response. All 9 subjects exhibit evidence of response on bone scan including two complete responses. Although most subjects did not have pain at baseline, one subject reported pain at baseline which resolved by Week 6. No dose reductions or interruptions have been reported to date, although one subject discontinued study treatment for fatigue that was present at baseline and another subject discontinued because of a pathologic fracture. This provides preliminary evidence that lower doses are pharmacologically active in a patient population with advanced CRPC.

Retrospective review of Phase 2 XL184-203 RDT: While the overall rate of dose reduction from 100 mg to 60 mg was 51%, only 14% required an additional reduction in dose from 60 mg to the next lowest dose of 40 mg, which is consistent with an overall improvement in tolerability profile at the 60-mg dose level. The majority (69%) of subjects with pain at baseline who experienced early dose reduction (before Week 6) to 60 mg went on to report pain improvement at Week 6. Moreover, 80% of these subjects remained progression-free and continued to report pain relief at the Week 12 time point. Thus the dose of 60 mg qd appears to offer improved tolerability while maintaining efficacy in a patient population with advanced CRPC and cancer-related pain at baseline.

Further analysis of the timing of AEs that led to dose reductions or interruptions was conducted. The median time to first AE triggering a dose reduction or interruption at 100 mg qd was 29 days, with very few subjects experiencing significant toxicity in the first 2 weeks of study treatment.

As such this study will adopt a starting cabozantinib dose of 60 mg qd. The goal of this regimen is to improve the overall tolerability of cabozantinib while maintaining efficacy in this patient population

2.4 CORRELATIVE STUDIES BACKGROUND

2.4.1 Circulating endothelial cells (CEC), circulating endothelial progenitor cells (CEP) and Circulating epithelial tumor cells (CTC)

CEC, CEP and CTC may serve as markers for assessment of treatment's antiangiogenic activity. CEC, CEP and CTC will be analyzed by multiparameter flow cytometry. Mononuclear cells will be isolated and run fresh or viably frozen. Immune subsets, including MDSC and Tregs, may be analyzed if sample permits.

2.4.2 c-Met analysis by real-time RT-PCR

The c-met proto-oncogene encodes a receptor tyrosine kinase (Met) and has been shown to play a role in oncogenesis. The clinical significance of Met in human bladder cancer was examined in bladder cancer cell lines and human bladder cancer tumors. The mRNA expression and genomic alteration of c-met was studied in five bladder cancer cell lines. Met overexpression was then compared with p53 nuclear accumulation (TP53) in primary bladder cancer (n = 142 patients). Expression of c-met tended to correlate with differentiation of cancer cell lines in the absence of point mutations. Expression of Met was positively associated with histologic grade, stage classification, tumor size, and nodular tumor growth (P <.05, respectively). Indicators for poor long-term survival were invasive cancer, multiple tumors, and Met overexpression (P =.0006, .01, and.04, respectively). In these studies, the c-met proto-oncogene demonstrated that it plays an important role in the progression of bladder carcinogenesis[28].

We hypothesize that the c-Met analysis by real-time RT-PCR correlates with the C-met level found in the serum and is of prognostic significance.

2.4.3 IL-8 circulating cytokine levels

IL-8 is a proinflammatory chemokine, which belongs to the chemokine receptors family and which stimulates neutrophil chemotaxis and degranulation[52,53]. IL-8 is a potent pro-angiogenic factor, which has been shown to initiate tumor angiogenesis in xenograft models in which VEGF signaling was regulated[54]. Its expression has been reported to enhance angiogenesis through the induction of MMP-9 and to induce metastases of human transitional cancer cell lines[55]. In animal models of urothelial cancer, high expression of IL-8 was associated with a significant increase in tumor growth and metastases[56] A recent study has associated increased IL-8 plasma levels in xenograft renal cell carcinoma (RCC) models with resistance to sunitinib treatment.[57] In the same study, IL-8 was overexpressed in tumors from patients refractory to sunitinib. Increased expression of IL-8, MMP-9, and VEGF in non-small-cell lung cancer patients, treated with the oral inhibitor of VEGFR2 tyrosine kinase vandetanib, correlated with a higher risk of progression.[58] In mRCC patients treated with pazopanib, baseline levels of IL-8 correlated with tumor burden,[59] and different polymorphisms of the IL-8 gene were significantly associated with treatment activity.[60] The role for IL-8 baseline levels as a predictive serum biomarker of sunitinib activity in patients with urothelial cancer was studied and it was found that low IL-8 baseline levels were significantly associated with increased time to progression.[61]

2.4.4 Genetic biomarkers

Single nucleotide polymorphisms (SNPs) in genes that play an important role in the drug metabolism and disposition of cabozantinib (via cytochrome P450 3A4 and ABCB1-mediated pathways) will be evaluated to correlate with efficacy and clinical outcomes. Functional SNPs in

the *VEGFR2* gene could alter antiangiogenic treatment response or outcome by affecting the VEGF signaling pathways. Thus, we will determine if *VEGFR2* genetic variants may be correlated to toxicity and clinical outcomes as we have previously shown in patients treated with bevacizumab and sorafenib[62].

2.4.5 Angiogenesis Markers

Plasma levels of several angiogenic biomarkers, including VEGF-A, soluble VEGFR2 (sVEGFR2), and placental growth factor (PIGF), have been shown to be significantly altered after single agent cabozantinib treatment (Investigator's brochure). Post-treatment changes in soluble MET (sMET), a potential biomarker for MET inhibition, were observed to be of statistical significance in clinical studies. Plasma samples will be obtained to measure changes in the molecular markers of angiogenesis, as well as sMET/KIT before and after administration of the combination. The potential relationship between biomarker expression and tumor response will be explored.

2.4.6 Plasma and urinary HGF and MET

We will collect urine and blood from patients on this study in order to determine whether urinary hepatocyte growth factor (HGF), urinary soluble MET receptor (sMet), plasma HGF and plasma Met levels are biomarkers of bladder cancer (transitional cell carcinoma; TCC) and/or response to systemic treatment with the experimental Met/VEGFR inhibitor cabozantinib. Soluble Met levels are determined by electrochemiluminescence immunoassay and normalized to urinary creatinine values.

2.4.7 Met expression in tissue

We will investigate the expression and prognostic role of the receptor tyrosine kinase MET, phosphorylated MET, and the ligand hepatocyte growth factor (HGF) in patients with urothelial cancer enrolled in this study. MET, pMET, and HGF expression will be assessed using immunohistochemistry. MET, pMET, and HGF will be correlated with extent of disease, therapy response rate, progression free and overall survival.

Tissue blocks and slides obtained from outside pathology departments will be analyzed as available. Tissue biopsies will be encouraged but done strictly on a voluntary basis. Biopsies will be obtained from primary tumor sites and/or metastatic sites.

2.4.8 Immune subsets and angiogenesis markers in plasma and tumor tissue

Circulating and intratumoral immune subsets and other markers of the microenvironment, hypoxia-inducible factor (HIF) 1α and 2α and other angiogenesis and/or immunologic markers will be analyzed at baseline and 8-18 weeks after treatment. At 8 weeks (after 2 cycles of treatment), the potential for biopsy will be discussed with the patient. Tissue blocks and slides obtained from outside pathology departments will be analyzed as available. Tissue biopsies will be encouraged but done strictly on a voluntary basis. Biopsies will be obtained from primary tumor sites and/or metastatic sites.

2.4.9 Imaging with PET/CT and optional PET/MRI:

Fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) has been approved for imaging in many malignancies but not for bladder cancer. A retrospective analysis FDG-PET/CT in patients with metastatic urothelial cancer demonstrated

that it has excellent sensitivity and specificity in the detection of metastatic bladder cancer[63]. FDG-PET/CT scans may provide better accuracy in clinical information for directing therapy. We will prospectively explore the utility of FDG-PET CT and FDG-PET MRI in this study.

2.4.10 Comparison of Target Lesion Volume/ Density and RECIST Measurements on CT of Metastatic Urothelial Cancer

At present, conventional imaging evaluation of tumor burden in metastatic disease is limited to axial measurements of select target lesions, which serves as a surrogate assessment for three dimensional changes in tumor size. Rigorous quantitative assessment of tumor response to cancer therapy is dependent upon assessment of these three dimensional changes in size. Recent image processing algorithms allow for formal RECIST reporting within clinical radiology reports, as well as tumor volumetric assessment and HU analysis within PACS and radiologist workflow. Advanced algorithms allow for rapid SA volumetric and tumor density measurements that more accurately reflect tumor burden/ treatment response compared to single dimensional axial measurements alone. Radiologists and information processing IP technologists can use PACS to record RECIST reports that include this information as accurate as existing team measurements. RECIST and volumetric analysis with data integrated has the potential to improve metastatic lesion quantification over existing reporting standards. Ability to produce RECIST and volumetric calculations in reports in PACS, RIS and HIS should improve quality of patient care in facilities treating cancer patients.

2.4.11 Quality of Life Assessment

In the second line setting, chemotherapy is given with the intent of hindering disease progression and prolonging quality of life. As more treatments for solid tumor malignancies evolve, particularly for the palliative setting, their efficacy will be measured and agents compared not only by the traditional overall and progression free survival standards, but by the effect upon patient quality of life[64]. "Symptom Inventory" developed by Charles Cleeland at MDACC is a questionnaire that attempts to assess the degree to which various symptoms "interfere with life." This cancer symptom measurement tool will be utilized at baseline and following cycle 3 of XL-184 to informally evaluate its impact upon health related quality of life parameters in this population, to better measure the benefit of therapy against the risk of decline is quality of life.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria

Cohort 1 only (urothelial progressive disease)

3.1.1.1 Patients must have a histologically confirmed diagnosis of urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis. Confirmation may be obtained from any CLIA certified lab.

3.1.1.2 Patients must have progressive metastatic disease. Progressive disease will be defined as new or progressive lesions on cross-sectional imaging.

3.1.1.3 Patients must have at least one measurable site of disease (according to RECIST (version 1.1) criteria)

Cohort 2 only (Bone-only)

3.1.1.4 Patients must have a histologically confirmed diagnosis of urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis. Confirmation may be obtained from any CLIA certified lab.

3.1.1.5 Patients must *not* have measurable progressive disease (RECIST 1.1)

3.1.1.6 Patient must have appearance of at least one new bone lesion.

Cohort 3 (Rare histologies)

3.1.1.7 Patient must have a histologically confirmed diagnosis of non-transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis including but not limited to squamous cell, neuroendocrine, adenocarcinoma including urachal and sarcomatoid. Confirmation may be obtained from any CLIA certified lab.

3.1.1.8 Patients must have progressive metastatic disease. Progressive disease will be defined as new or progressive lesions on cross-sectional imaging.

3.1.1.9 Patients must have at least one measurable site of disease (according to RECIST (version 1.1) criteria)

All cohorts

3.1.1.10 Patients must have been previously treated, as defined by treatment with at least one prior cytotoxic regimen or agent.

3.1.1.11 Age ≥ 18 years. Because no dosing or adverse event *data are cu*rrently available on the use of cabozantinib in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.1.1.12 ECOG performance status ≤2 (Karnofsky ≥60%, (see **Appendix A**)

3.1.1.13 Adequate organ function as defined by the following criteria:

- Hemoglobin ≥ 9 g/dL
- Absolute neutrophil count (ANC) ≥ 1500/μL
- Platelets ≥ 75,000/μL
- Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤3.0 x upper limit of normal (ULN); ≤ 5.0 x ULN in cases of liver metastases
- Total serum bilirubin ≤ 1.5 × the upper limit of normal (ULN). For subjects with known Gilbert's disease or similar syndrome with slow conjugation of bilirubin, total bilirubin ≤ 3.0 mg/dL
- Serum creatinine ≤ 1.5 X institutional upper limits of normal or for patients with creatinine levels above 1.5 x institutional normal: creatinine clearance ≥ 50 mL/min/1.73 m^2 by 24 hour urine collection or estimated creatinine clearance of ≥ 50 mL/min. For creatinine clearance estimation , the Cockcroft and Gault equation should be used:
  - Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72)
  - Female: Multiply above result by 0.85

- Urine protein/creatinine ratio (UPCR) ≤ 2

3.1.1.14 Patient must be able to provide either archival tumor samples (H&E slides and one paraffin block or 10 unstained slides) or undergo tumor biopsy.

3.1.1.15 Patient must be capable of understanding and complying with protocol requirements and is willing to give informed consent

3.1.1.16 The effects of XL184 on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (see below) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of XL184 administration.

Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (*e.g.*, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s).

3.1.1.17 Women of childbearing potential must have a negative pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Postmenopause is defined as amenorrhea ≥ 12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression or any other reversible reason.

3.1.2 Exclusion Criteria

3.1.2.1 The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 3 weeks, or nitrosoureas or mitomycin within 6 weeks before the first dose of study treatment.

3.1.2.2 Prior treatment with cabozantinib

3.1.2.3 Prior treatment with other small molecule inhibitors of VEGFR within ≤ 2 years of study enrollment.

3.1.2.4 The subject has received radiation therapy:

- to the thoracic cavity or gastrointestinal tract within 3 months before the first dose of study treatment
- to brain metastases within 14 days before the first dose of study treatment
- to any other site(s), with the exception of bone, within 28 days before the first dose of study treatment

3.1.2.5 The subject has received radionuclide treatment within 6 weeks before the first dose of study treatment

3.1.2.6 The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 14 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment.

3.1.2.7 The subject has received any other type of investigational agent within 28 days before the first dose of study treatment.

3.1.2.8 The subject has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia and other non-clinically significant AEs.

3.1.2.9 The subject has a primary brain tumor

3.1.2.10 The subject has active brain metastases, leptomeningeal or epidural disease (Note: Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible. Neurosurgical resection of brain metastases or brain biopsy is permitted if completed at least 3 months before starting study treatment. Baseline brain scans are not required to confirm eligibility.)

3.1.2.11 The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 7 days before the first dose of study treatment.

3.1.2.12 The subject requires treatment, in therapeutic doses, with oral anticoagulants such as warfarin prior to initiation of protocol therapy. Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and low molecular weight heparin (LMWH) are permitted. Subjects will be permitted to use anticoagulation as described in section **5.2.2.6** if treatment is required while they are enrolled on the protocol.

3.1.2.13 The subject requires chronic concomitant treatment of strong CYP3A4 inducers (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/ medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Please refer to patient information sheet in **Appendix B**.

3.1.2.14 The subject has experienced any of the following within 3 months before the first dose of study treatment:

- clinically-significant hematemesis or gastrointestinal bleeding
- hemoptysis of ≥ 0.5 teaspoon (≥2.5 mL) of red blood
- any other signs indicative of pulmonary hemorrhage

3.1.2.15 The subject has tumor invading (or concern for invasion) major blood vessels

3.1.2.16 Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the

judgment of the Investigator would make the patient inappropriate for entry into this study.

3.1.2.17 The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.

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

a. Cardiovascular disorders including

i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening

ii. Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening)

iii. Any history of congenital long QT syndrome

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

- unstable angina pectoris
- clinically-significant cardiac arrhythmias
- stroke (including TIA, or other ischemic event)
- myocardial infarction

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

i. Any of the following within 28 days before the first dose of cabozantinib

- active peptic ulcer disease,
- active inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
- active malabsorption syndrome

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

(1) abdominal fistula

(2) gastrointestinal perforation

(3) bowel obstruction or gastric outlet obstruction

(4) 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 than 6 months ago.

c. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy.

d. Other clinically significant disorders such as:

i. No active systemic infection requiring parenteral antibiotics

ii. serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment

iii. history of organ transplant

iv. concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment

v. history of major surgery as follows:

(1) Major surgery within 3 months of the first dose of cabozantinib if there were no wound healing complications or within 6 months of the first dose of cabozantinib if there were wound complications.

(2) Minor surgery within 1 months of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications

In addition, complete wound healing from prior surgery must be confirmed at least 28 days before the first dose of cabozantinib irrespective of the time from surgery

3.1.2.19 The subject is unable to swallow tablets

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

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

3.1.2.22 The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

3.1.2.23 The subject has had within 2 years before the start of study treatment evidence of another malignancy which required systemic treatment

3.1.2.24 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the study agents. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.1.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this trial.

3.1.3.1 Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	4	=	6
Not Hispanic or Latino	15	+	44	=	59
Ethnic Category: Total of all subjects	**17 (A1)**	**+**	**48 (B1)**	**=**	**65 (C1)**
Racial Category					
American Indian or Alaskan Native	0	+	1	=	1
Asian	3	+	4	=	7
Black or African American	4	+	9	=	13
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	10	+	33	=	43
Racial Category: Total of all subjects	**17 (A2)**	**+**	**48 (B2)**	**=**	**65 (C2)**
	(A1 = A2)		(B1 = B2)		(C1 = C2)

3.1.4 Recruitment Strategies

The study will be posted on the CCR website and on clinicaltrials.gov

3.2 SCREENING EVALUATION

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening before study treatment administration. Screening evaluations may be performed as part of an NIH Screening protocol. This does not include the baseline correlative studies that will only be performed after the patient has signed the consent form.

The following assessments will be conducted prior to subjects receiving their first dose of cabozantinib on this protocol:

- History including performance status assessment
- Physical examination including height, weight, vital signs
- Laboratory assessments: acute care panel (sodium, potassium, chloride, total CO2 (Bicarbonate), creatinine, glucose, urea nitrogen), mineral panel (albumin, calcium total, magnesium total, phosphorus), hepatic panel(alkaline phosphatase, ALT/GPT, AST/GOT, total bilirubin, direct bilirubin), ionized calcium, amylase, lipase, LDH, total protein, GGT
- 24 hour urine collection if needed (see section **3.1.1.13**)
- Urinalysis including UPCR
- PT/INR, PTT
- Thyroid function tests – TSH, total T3, T4

- 12 lead ECG
- Urine or serum HCG (in women of childbearing potential)
- CT Scan of chest, abdomen and pelvis (MRI may be performed in subjects unable to tolerate contrast for CT)
- Pathology evaluation/confirmation of urothelial carcinoma

4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4.1 TREATMENT ASSIGNMENT PROCEDURES

Cohorts

Number	Name	Description
1	*Cohort 1 (urothelial progressive disease)*	*Patients with urothelial progressive disease of the bladder, urethra, ureter, or renal pelvis.*
2	*Cohort 2 (Bone-only)*	*Patients with bone-only urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis.*
3	*Cohort 3 (Rare histologies)*	*Patients with non-transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis including but not limited to squamous cell, neuroendocrine, adenocarcinoma including urachal and sarcomatoid.*

Arms

Number	Name	Description
1	*Cabozantinib*	*Administered orally at a dose of 60 mg once daily on each day of a 28-day cycle.*

Randomization and Arm Assignment

Patients in all cohorts are assigned to arm 1.

5 TREATMENT PLAN

This is a Phase 2, single-arm, open-label study of cabozantinib in subjects with advanced/metastatic urothelial carcinoma that has progressed despite treatment with cytotoxic chemotherapy. The primary endpoint is to determine the activity of cabozantinib as determined by response rate. A Simon 2-stage design will be used. In the first stage, 21 subjects will be

accrued. If there are at least 2 responses, accrual will continue to the second stage and an additional 20 evaluable subjects will be enrolled. If there are a total of 6 or more responses among the total of 41 evaluable subjects, Cabozantinib will be considered of clinical interest in progressive urothelial carcinoma.

The primary objective of the study will be to determine the activity of cabozantinib as determined by progression free survival by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Cabozantinib will be administered orally at a daily dose of 60 mg. Patients may continue on study as long as they are tolerating therapy. Patients who achieve and maintain a response of CR by RECIST per section **11.1.4.4** for over 3 years, may have the drug held (drug holiday) as described in section **6.2**.

5.1 AGENT ADMINISTRATION

5.1.1 Cabozantinib

Treatment will be administered primarily on an outpatient basis. Subjects will be instructed to take cabozantinib orally at a dose of 60 mg once daily on each day of a 28 day cycle. If a dose is missed, subjects should be instructed *not* to make it up on the following day. Cabozantinib should be taken on an empty stomach; patients must fast for 2 hours before and 1 hour following each dose of cabozantinib. Subjects should be instructed not to crush or chew and to avoid both grapefruit and Seville orange products while on the study drug.

Patients will be provided a pill diary (**Appendix C**) to track the oral study agents, instructed in its use, and asked to bring it with them to each appointment. A new copy of the pill diary will be given to patients whose dose is reduced due to adverse events. Pill counts will also be maintained by study personnel.

Subjects will be instructed to notify their physician immediately of any and all AEs. 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.

Reported adverse events and potential risks are described in Section **0**. Appropriate dose modifications are described in Section **6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Cabozantinib	none	60 mg	PO	Daily	28 days (4 weeks)

Patients who tolerate cabozantinib at 60 mg daily during the first 2 cycles (first restaging time period) without ≥ grade 2 toxicity may undergo dose escalation to 80 mg daily at the discretion of the Principal Investigator.

5.1.2 Study Drug Accountability & Compliance

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice.

The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt (compliance form available in **Appendix D**). In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be returned to the NCI Clinical Repository for proper destruction as per the NCI guidelines.

Drug accountability and subject compliance will be assessed with drug dispensing and return records.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of XL184 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.2.1 Concurrent Medications/Interventions

5.2.1.1 Anticancer therapy

If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (*e.g.*, palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

5.2.1.2 Other Medications

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution.

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically prior to the first dose of study treatment.

No concurrent investigational agents are permitted.

5.2.1.3 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 (*i.e.*, 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 (*e.g.*, 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 (*e.g.*, chronic use of modafinil) should be avoided because of its potential to reduce cabozantinib exposure. 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 (*e.g.*, 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 (*e.g.*, CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.

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/.

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 (*e.g.*, 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.

Drugs Associated with QTc Prolongation: Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

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 H2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs and H2-antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of PPIs (*e.g.*, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (*e.g.*, 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

5.2.2 Supportive Care

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Sections **6.1.1** and **6.1.2**, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, skin disorders (PPE), embolism and thrombus, and hypertension, see below.

5.2.2.1 Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. 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[65]. 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 2**. 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 not including cabozantinib, high fat meals and alcohol.

5.2.2.2 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 Section **6.1.1** if antiemetic treatment and/or prophylaxis alone is not adequate.

Agents classified as having the highest therapeutic index (such as 5-HT3 receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or dexamethasone are recommended[66-68]. 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.

5.2.2.3 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.

5.2.2.4 Hepatobiliary Disorders

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. See section **6.1.4** for additional information.

5.2.2.5 Skin Disorders

All subjects on study should be advised on prophylactic measures for hand-foot syndrome including the use of emollients (Ammonium lactate 12% cream or heavy moisturizer twice daily), 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.

Urea 20% cream twice daily and clobetasol 0.05% cream once daily should be used in subjects that exhibit toxicity. NSAIDS, GABA agonists and opioids may be used for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. 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.

5.2.2.6 Embolism and Thrombosis

Low molecular weight heparin should be used to establish full anticoagulation in subjects on the first occurrence of a PE and/or DVT. Full anticoagulation with warfarin is not permitted and venous filters are not recommended. Treatment can be restarted at the discretion of the investigator. 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.

5.2.2.7 Hypertension

See instructions in section **6.1.8**.

5.3 On Study Assessments

Please see study calendar (section **10**) for schedule of the study assessments.

5.3.1 Electrocardiogram (ECG) Assessments

ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures. Pre-treatment ECGs should be performed after vital signs are obtained and before any blood draws. At any time point, if there is an increase in QTc interval to an absolute value > 500 msec using the Fridericia correction formula, two additional ECGs should be performed approximately 2 minutes apart, within 30 minutes. If the average QTc interval calculated by the Fridericia formula from the three ECGs is > 500 msec, study treatment must be withheld and a cardiology consultation is recommended for evaluation and subject management. Study treatment may only be continued if the QTc resolves to 500msec or less and per investigator judgment that continued treatment is appropriate. Abnormalities in the ECG that lead to a change in subject management (eg, dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs. When an ECG time point coincides with other activities, the ECG will be collected first, followed by vital signs.

5.3.2 Vital Signs

Vital signs (body temperature, respiratory rate, and blood pressure and pulse) will be conducted at regular intervals. Blood pressure and pulse will be measured after the subject has been sitting for at least 5 minutes.

When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled time point, and the vitals will be obtained as close to the scheduled blood draw as possible.

5.3.3 Physical Examinations

A physical examination will include assessments of general appearance, skin, HEENT, thorax/lungs, cardiovascular, abdominal, genitourinary, musculoskeletal and neurological findings. Any pertinent findings should be documented either in the subject's medical history (if determined to be prior to the first dose of cabozantinib) or as an AE (if new or worsening after the first dose of cabozantinib).

5.3.4 Laboratory Assessments

Laboratory assessments will include the following:

5.3.4.1 Hematology:

- CBC with differential
- Reticulocytes (if indicated)
- Erythrocyte sedimentation rate (if indicated)

5.3.4.2 Serum chemistries:

- Hepatic panel (alkaline phosphatase, ALT/GPT, AST/GOT, total bilirubin, direct bilirubin)
- Acute care panel (sodium, potassium, chloride, total CO2 (Bicarbonate), creatinine, glucose, urea nitrogen)
- Mineral panel (albumin, calcium total, magnesium total, phosphorus)
- Ionized calcium
- Amylase
- Lipase
- Lactate dehydrogenase (LDH)
- Total protein
- γ-glutamyltransferase (GGT)

5.3.4.3 Urinalysis including urine creatinine and UPCR

5.3.4.4 Thyroid function tests - TSH, total T3 and T4

5.3.4.5 PT/INR or PTT

5.3.4.6 24 hour urine collection for protein

5.3.4.7 Urine or serum HCG (in women of childbearing potential)

5.4 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (unless patients are on drug holiday in which case disease progression will prompt resuming the treatment),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Necessity for treatment with other anticancer treatment prohibited by the protocol,
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment,
- Women who become pregnant or are breast feeding,
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol, or
- Significant noncompliance with the protocol schedule in the opinion of the investigator.
- The minimum dose of study treatment will be 20 mg once per day. Subjects who cannot tolerate 20 mg once per day will have study treatment discontinued.

5.5 DURATION OF FOLLOW UP

Patients will be contacted by telephone 30 – 37 days after the last dose of cabozantinib for a safety assessment. Patients on drug holiday do not need to be contacted.

Any study drug remaining in the patient's possession at this time will be returned by mail and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this phone call, and for subjects with SAEs related to study treatment that occur after the time of this phone call.

The Investigator or designees will make every possible attempt every 2 months (±7 days) after the follow-up phone call to contact the patient or family to obtain the survival information of the patient and start date of additional anticancer treatment.

5.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety phone call approximately 30 days following the last dose of study therapy.

5.6.1 Criteria for removal from protocol therapy

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

In addition, any of the following conditions unless they occur during the drug holiday require withdrawal of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from treatment
- Hemorrhage within 30 days of agent administration
- Necessity for treatment with other investigational drug or other anticancer medications prohibited by protocol
- Noncompliance with the protocol schedule
- Participation in another clinical study using anticancer agent(s)
- Occurrence of any grade 4 non hematologic AE unless the subject is unequivocally deriving clinical benefit
- Occurrence of grade 4 febrile neutropenia unless the subject is unequivocally deriving clinical benefit
- Inability to tolerate a 20 mg daily dose of cabozantinib
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment
- Women who become pregnant or are breast feeding
- Cabozantinib treatment delays > 6 weeks unless the subject was unequivocally benefitting from cabozantinib treatment
- Progressive disease (PD)
- Investigator Discretion

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol-specified follow-up procedures and end-of-treatment assessments, if possible, unless consent to participate in the study is also withdrawn.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

5.6.2 Off Study Criteria

- Investigator Discretion
- Manufacturer no longer able to supply study agent
- Participant requests to be withdrawn from study

- Death

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

5.6.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is off protocol therapy and when a subject is taken off-study. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 CABOZANTINIB

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study treatment and for any serious adverse event (SAE) assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the last dose of study treatment.

Subjects will be instructed to notify their physician immediately of any and all AEs. 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.

General guidelines for the management of non-hematologic and hematologic toxicities are provided in section **6.1.1** and section **6.1.2**, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinurea, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate section below. Guidance for the management of fatigue, anorexia, weight loss, 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 Cabozantinib Investigator's Brochure.

Re-escalating study treatment after a dose reduction:

- Subjects who required a dose reduction for Grade 4 non-hematologic toxicity should not be re-escalated
- For other related AEs, subjects may be re-escalated to the previous dose at the discretion of the investigator but not sooner than 2 weeks after resolution to Grade ≤ 1 or to the baseline value of AEs.

- If a subject has been dose-reduced more than once, dose re-escalation can only occur to the next higher dose level. Further dose escalation to higher well-tolerated dose levels is allowed only if clinically indicated per investigator's judgment and dose escalation criteria are met with each escalation (e.g. a minimum 2 week interval between escalations)
- If the AEs that previously led to dose reduction(s) recur upon re-escalation, the dose should be reduced again and no further dose escalation will be permitted.
- Dose re-escalation is not allowed for dose reduction triggered by neutropenia or thrombocytopenia.

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.

Dosing delays and modification instructions for cabozantinib hematologic and non-hematologic toxicities are below. Please consult **Table 2** for the appropriate dose at each dose reduction. 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.

If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity. Baseline CT and bone scans must be repeated at the time the study drug is reinitiated.

The minimum dose of study treatment will be 20 mg daily. Subjects who cannot tolerate 20 mg daily will have study treatment discontinued.

Table 2: Dose Levels

Dose Level	Cabozantinib dose
-2	20 mg
-1	40 mg
1	60 mg
2	80 mg

The reason for treatment delay and reduced dose must be recorded on the case report form (CRF).

6.1.1 General Guidelines for other Non-Hematologic Toxicities

CTCAE Version 5 Grade	**Guidelines/Intervention**
Grade 1:	Add supportive care as indicated. Continue study treatment at 60 mg daily.

CTCAE Version 5 Grade	Guidelines/Intervention
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 60 mg daily.
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	Dose reduce • If the AE dose not resolve to Grade ≤ 1 or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. • If the AE resolves to Grade ≤ 1 or baseline without a dose interruption, continue the reduced dose.
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.	

6.1.2 Hematologic Toxicities

CTCAE Version 5 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 one dose level reduction.
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 one dose level reduction
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 one dose level reduction.
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 and sponsor, but only with sponsor approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly 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 and sponsor and only with approval by the sponsor.
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.

ANC, absolute neutrophil count; LLN, lower limit of normal
Neutropenia: Grade 1 (LLN ≤ ANC < 1.5 × 10^9/L; Grade 2 (1 × 10^9/L ≤ ANC <1.5 x 10^9/L),
Grade 3 (0.5 × 10^9/L ≤ ANC < 1 × 10^9/L), Grade 4 (ANC < 0.5 × 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 × 10^9/L); Grade 4 (Platelet count < 25 x 10^9/L).

No dose modifications are required for grade 1, grade 2 or other grade 3 hematological toxicities.

6.1.3 Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

6.1.3.1 Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. 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 (Benson *et al.,* 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1 should be followed. 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.

6.1.3.2 Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table **6.1.1** should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

6.1.3.3 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 (*e.g.*, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

6.1.4 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:

Transaminase elevation CTCAE v5.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib 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 cabozantinib 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 cabozantinib 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 cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
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 of cabozantinib as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly 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 increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	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 and sponsor but only with sponsor approval.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, 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 ≤ baseline grade).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2 ×ULN), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase) 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.

6.1.5 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 has 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). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

6.1.5.1 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 or Grade 4 elevations recur, then treatment must be interrupted again until 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.

6.1.5.2 Pancreatitis

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and 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 at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval.

6.1.6 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 in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures includes the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (*e.g.*, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or 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.

Treatment guidelines for PPE related to study treatment are presented in the table below.

In the case of study treatment-related skin changes (*e.g.*, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the 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.

6.1.6.1 Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose. 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.
Grade 2	If tolerable, continue cabozantinib at current dose. If intolerable, reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. If treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a treatment interruption is again required, the dose must be reduced when treatment resumes. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, proceed to the management guidelines for Grade 3 PPE.
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

6.1.7 Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. 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.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

6.1.8 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. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. 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 ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (see next Table below).

6.1.8.1 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, or if the subject is symptomatic, the 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.

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
≥ 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.
Hypertensive crisis or hypertensive encephalopathy	Discontinue all study treatment
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	

Patients with a history of hypertension should be instructed to record their blood pressure once per week during each cycle of cabozantinib on the form provided in **Appendix E** and to bring the form with them at each clinic visit.

6.1.9 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 2, 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 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) 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 the next Table below.

Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 2	• No change in treatment or monitoring
> 2 and < 3.5	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week. If UPCR is < 2 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).

Urine Protein/Creatinine Ratio	Action To Be Taken
≥ 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 < 2.5, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 2, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

6.1.10 Guidelines for the Prevention of Hemorrhagic Events

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 with cavitations or tumor lesions which invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases 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 (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥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 at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors invading a major blood vessel while on study treatment must be discontinued from cabozantinib treatment.

6.1.11 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.

6.1.12 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:

6.1.12.1 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.

6.1.12.2 Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs 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.

6.1.13 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.

6.1.14 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 (see Cabozantinib Investigator's Brochure). 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 (*e.g.*, 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 required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

6.1.15 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. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. 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.

6.1.16 Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org)
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).

- Medical conditions which can alter electrolyte status e.g., severe or prolonged diarrhea.

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (*e.g.*, after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

6.2 CABOZANTINIB DRUG HOLIDAY

Patients who achieve a complete response by RECIST lasting > 3 years, can have study therapy held (drug holiday) until they relapse. Scan intervals for patients achieving a complete response for > 3years will be changed from every 8 weeks to every 12 weeks. At the time of progressive disease, cabozantinib will be resumed and scan showing progressive disease will become the new baseline scan.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section **7.1**) and the characteristics of an observed AE (Section **7.2.1.1**) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR)

7.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) XL184 (Cabozantinib s-malate, NSC 761968)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3219 patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 17, 2018[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
	Voice alteration		***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism

EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); Portal vein thrombosis

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; Skin ulceration

VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 DEFINITIONS

7.2.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.2.1.1 Adverse Event Characteristics:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section **7.1.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.2.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.2.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- 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.

7.2.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.2.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.2.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.2.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.2.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 EXPEDITED ADVERSE EVENT REPORTING TO CTEP

7.3.1 Reporting via CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section **7.3.3**).

7.3.2 In the Event of Lost Internet Connectivity

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require

hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 ROUTINE ADVERSE EVENT REPORTING TO CTEP

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 NIH INTRAMURAL IRB AND CLINICAL DIRECTOR REPORTING

7.5.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.5.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NIH Intramural IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    NOTE: Grade 1 events are not required to be reported.

7.5.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

7.6 SECONDARY MALIGNANCY

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 SECOND MALIGNANCY

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7.8 DATA AND SAFETY MONITORING PLAN

7.8.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.8.2 Sponsor Monitoring Plan

See section **12.3.1**.

8 PHARMACEUTICAL AND IMAGING AGENT INFORMATION

8.1 CABOZANTINIB (XL184) (NSC 761968)

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

Other Names: Cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: C28H24FN3O5.C4H6O5 **M.W.:** 635.6

Mode of Action: XL184 inhibits multiple RTKs implicated in tumor growth (progression of tumors in bone), metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

How Supplied: XL184 is supplied by Exelixis and distributed by the DCTD. XL184 is available in 20 mg and 60 mg tablet. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.

XL184 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

Storage: Store intact bottles at controlled room temperature, 20^0 to 25^0C.

Stability: XL184 should be dispensed in its original container. XL184 tablets are stable for up to 24 hours when dispensed in an open container, such as in a pill cup, and are stable for up to 7 days when dispensed in a closed container, such as a pharmacy dispensing bottle.

Route of Administration: Oral.

Method of Administration: Take cabozantinib on an empty stomach, (fasting is required 2 hours before and 1 hour after each cabozantinib dose). Do not crush or chew.

Potential Drug Interactions: XL184 is a substrate of CYP3A4. Coadministration of XL184 with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Examples of strong CYP3A4 inducers are rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, Phenobarbital, and St. John's Wort. Strong CYP3A4 inhibitors are ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications. Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

In vitro data, XL184 is not a P-gp substrate but may inhibit the P-gp transport activity.

XL184 is highly protein bound, 99.9%. Use caution when coadminister XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Avoid concomitant use of XL184 with proton pump inhibitors (PPIs) and H_2 -antagonists if possible. The PPIs and H_2 –antagonists decrease XL184 plasma exposure levels and its effectiveness in vivo. Examples of PPIs are omeprazole, lansoprazole, rabeprazole, pantoprazole,

and esomeprazole; examples of H_2 –antagonists are ranitidine, famotidine, and nizatidine. Cimetidine is a moderate CYP3A4 inhibitor. Avoid using cimetidine with XL184. If antacids, H_2 blockers, or PPIs are needed, take them at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

Patient Care Implications: Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Cimetidine or omeprazole is also available over-the-counter (OTC). Do not use cimetidine. If need an antacid, take it at least 2 hours (preferably 4 hours) after taking XL184 but at least 14 hours before the next dose of XL184 if possible.

Availability

XL184 (cabozantinib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

XL184 (cabozantinib) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section **12.5**).

8.1.1 Agent Ordering and Agent Accountability

8.1.1.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.1.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

(Please see **Appendix F** for the blood and tissue collection schedule in chart form)

9.1 BIOMARKER STUDIES

All collection pre-treatment collection times are within 5 days prior to treatment; all other collection times and within ± 5 days of stated collection. The blood biomarker studies will be prioritized as follows: Plasma HGF and MET, VEGF levels, immune subset, genetic biomarker, IL-8 circulating cytokine levels, c-Met analysis by real-time RT-PCR and CTC/CEC.

9.1.1 Circulating endothelial cells (CEC), circulating endothelial progenitor cells (CEP) and Circulating epithelial tumor cells (CTC)

CEC, CEP and CTC will be analyzed by multiparameter flow cytometry. Mononuclear cells will be isolated and run fresh or viably frozen. Immune subsets, including MDSC and Tregs, may be analyzed if sample permits.

9.1.1.1 Collection & Handling of Specimens:

Collect 2 times: at C1D1 pre-treatment and C3D1 pre-treatment

Draw whole blood into three 8 mL BD Vacutainer Cell Preparation Tube (CPT) with Sodium Citrate and two 10 mL EDTA lavender top tubes.

- Immediately after collection, mix the blood sample by gentle inversion several times.
- The date and exact time of each blood draw should be recorded on the tube.
- Please email Jane.Trepel@nih.hhs.gov, lees@pop.nci.gov and leemin@mail.nih.gov about expected samples and call Jane Trepel's lab at 240-760-6330 to arrange for immediate pick-up.

9.1.1.2 Site Performing the Assay

The assays will be performed by Dr. Min-Jung Lee and Dr. Yeong Sang Kim in Jane Trepel's laboratory in the Medical Oncology Branch, Building 10, Room 12N218.

9.1.2 c-Met analysis by real-time RT-PCR

9.1.2.1 Collection & Handling of Specimens:

- Peripheral blood for analysis of c-Met mRNA will be collected in a PAXgene tube on C1D1 pre-treatment and C3D1 pre-treatment
- (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions.
- After the blood is drawn, the tube should be inverted several times, placed at 4°C. RNA will be isolated using the PAXgene Blood RNA Kit according to the manufacturer's instructions. The first strand cDNA will be synthesized from total RNA by using a HC reverse transcription kit (Applied Biosystems). The reaction mixture is diluted to 100 µL with TE. PCR will be performed using the c-met primers).
- Please email Jane.Trepel@nih.hhs.gov, lees@pop.nci.gov and leemin@mail.nih.gov 24 hours prior to anticipated collection and call Jane Trepel's lab at 240-760-6330 to arrange for immediate pickup when drawn.

9.1.2.2 Site Performing the Assay

cMet mRNA levels in peripheral blood will be analyzed by the Trepel Lab, Medical Oncology Branch, Building 10, Room 12N218.

9.1.3 IL-8 circulating cytokine levels

We will be collecting blood samples to determine whether IL-8 levels are associated with cabozantinib treatment outcome measures.

9.1.3.1 Collection & Handling of Specimens:

- Peripheral blood will be drawn in a 5 mL red top tube pretreatment on C1D1, cycle 1 day 15 and at cycle 2 day 1.
- The date and exact time of each blood draw should be recorded on the tube.
- Please email Jane.Trepel@nih.hhs.gov, lees@pop.nci.gov and leemin@mail.nih.gov 24 hours prior to anticipated collection and call Jane Trepel's lab at 240-760-6330 to arrange for immediate pickup when drawn.

9.1.3.2 Site Performing the Assay

Il-8 levels in peripheral blood will be analyzed using the ELISA technique by the Trepel Lab, Medical Oncology Branch, Building 10, Room 12N218

9.1.4 Genetic biomarkers

We will determine if *VEGFR2* genetic variants may be correlated to toxicity and clinical outcomes as we have previously shown in patients treated with bevacizumab and sorafenib[62].

9.1.4.1 Collection and Handling of Specimens

- One 10 mL EDTA lavender top tube will be collected on day 1 of cycle 2.
- Immediately after collection, invert the blood tube 8-10 times.
- Place the tube on wet ice and then store at 4° C in the refrigerator until processing.
- The date and exact time of each blood draw should be recorded on the tube.
- Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for immediate pickup.

9.1.4.2 Site Performing the Assay

These studies will be done by the Molecular Pharmacology Program, under the direction of Dr. Figg.

9.1.5 Angiogenesis Markers

Plasma levels of several angiogenic biomarkers, including VEGF-A, soluble VEGFR2 (sVEGFR2), and placental growth factor (PIGF), have been shown to be significantly altered after single agent cabozantinib treatment (Investigator's brochure).

The analysis will be done with assays developed on electrochemiluminescence platform that provides ultra-high sensitivity and very large signal dynamic range.

9.1.5.1 Collection and Handling of Specimens

Serum VEGF

- Collect on cycle 1 day 1 pretreatment, cycle 1 day 15 pretreatment, cycle 2 day 1 and at the time of progression.
- Venous blood samples will be collected in one 6mL EDTA tube per protocol time points.
- Immediately after collection, invert the EDTA tube 2-4 times and place the tube on wet ice and store at 4°C in the refrigerator until processing for a maximum of 30-60 minutes.
- The date and exact time of each blood draw should be recorded on the tube.
- Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for immediate pick-up.

9.1.5.2 Sample Processing

Upon arrival in the Blood Processing Core (BPC), blood samples will be centrifuged for 5 minutes at 1200 x *g*, at 4°C. The serum will be transferred into two cryovials and immediately frozen. Serum samples will be stored at -80°C until the time of analysis.

9.1.5.3 Site Performing the Assay

These studies will be done by the Molecular Pharmacology Program, under the direction of Dr. Figg.

9.1.6 Plasma and Tissue HGF and MET and urinary MET and spot creatinine

To determine whether urinary hepatocyte growth factor (HGF), urinary soluble MET receptor (sMet), plasma HGF and plasma Met levels are biomarkers of bladder cancer (transitional cell carcinoma; TCC) and/or response to systemic treatment with the experimental Met/VEGFR inhibitor cabozantinib.

In *fresh frozen tissue* (FFT), HGF, and the cabozantinib targets MET, phosphoMET, VEGFR2, RET, KIT, AXL and FLT3 will be quantitatively analyzed using two-site electrochemiluminescent immunoassays developed for use with a Meso Scale Discovery (MSD) SectorImager 2400 plate reader at baseline from patients on study with cabozantinib. Use of purified recombinant protein standards permits quantitation of receptor mass per mass total extracted cell protein.

9.1.6.1 Sample Collection Protocols

A. <u>URINE SAMPLES</u>

1. Collect at least 2 mL of urine prior to treatment at every visit while on study The source of the urine will need to be documented i.e. normally voided urine, without internal stent, Foley, percutaneous nephrostomy, ileal conduit, Indian pouch or neobladder.
2. Determine urine creatinine values per standard clinical laboratory testing protocol.
3. The date and exact time of the urine collection should be recorded on the tube.
4. Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for immediate pick-up.
5. sMet analysis requires 1-2 ml per sample. Adjust urine to pH 7.5 with Trizma-HCl (Sigma, St. Louis, MO), 2 mol/L, pH 7.5 using 50 microliters per 2 ml urine volume.

6. Centrifuge urine samples at 3000 x g for 10 min at room temperature to remove cells and debris; store samples in appropriately sized plastic cryovials (Nunc or Sargent; bar coded vials are preferred for optimal sample identification) at -80°C.

B. PLASMA SAMPLES

1. Blood samples should be collected in a 3 mL EDTA tube at every visit while on study.
2. The date and exact time of the urine collection should be recorded on the tube.
3. Blood samples should be centrifuged within 30 min at 1,300 RCF at room temperature for 10 minutes. Do not use braking to stop the centrifuge. This will give three layers: (from top to bottom) plasma, leucocytes (buffy coat), erythrocytes.
4. Carefully aspirate the supernatant (plasma) at room temperature and transfer to a new centrifuge tube. Take care not to disrupt the cell layer or transfer any cells.
5. Inspect the plasma for turbidity. Turbid samples should be centrifuged and the clarified supernatant should be transferred to cryovials and stored at –80°C. Ensure that the cryovials are properly labeled.
6. Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for immediate pickup.

C. FRESH TISSUE SAMPLES

1. A post treatment biopsy (as referenced in section **9.1.8.1.2**) will be performed on a voluntary basis, and cabozantinib target levels will be compared to baseline measurements on fresh tissue (see collection in section **9.1.7**). MET and HGF expression by IHC will be compared to MET, phosphoMET, and HGF expression by quantitative two-site electrochemiluminescent immunoassay. Results will be correlated with baseline prognostic factors such as tumor grade, stage, size, sites of metastatic disease, response to prior cisplatin therapy, response to cabozantinib, progression free survival and overall survival.
2. Please contact Dr. Bottaro to notify of biopsy date and time (301-402-6499) and to arrange for pick up of sample during biopsy.
3. Fresh tissue samples should be collected in empty cryovials on dry ice. The minimum tissue volume required for HGF or Met analysis is 50 ul (approx 50 ug); analysis for phospho-Met requires 100 ul.
4. The interval between sample acquisition and freezing on dry ice must not exceed 2 minutes. Frozen, vialed samples should be transferred to -80°C storage within 2 hours. Stored vials must be bar coded ONLY for sample identification.

9.1.6.2 HGF and Met Electrochemiluminescent Immunoassay Protocols

A. DETECTION OF HUMAN MET ECTODOMAIN (sMet)

1. Block with I Block solution (1X) 300 ul/well for 1 h at RT. Use 300 ul multi-channel pipette and disposable trough.
2. Wash 3 times with 150ul/well Ca^{2+}/Mg^{2+} free PBS.
3. Add capture antibody at 5 ug/ml, 25 ul/well and shake for 1 h.
4. Put out 20 previously frozen samples to thaw on ice at this time.
5. Wash 3 times with 150ul/well Ca^{2+}/Mg^{2+} free PBS.
6. Add samples and standards at 25 ul/well for 1 h with shaking. Adding the standards first; when the standards are done, mix the thawed samples well before adding to wells. If volume is insufficient to fill triplicate wells at 25 ul/well, note any lesser amount added.
7. Wash 3 times with 150ul/well Ca^{2+}/Mg^{2+} free PBS.
8. Add detection antibody at 1ug/ml, 25 ul/well for 1 h with shaking.
9. Wash 4 times with 150ul/well Ca^{2+}/Mg^{2+} free PBS.
10. Set up the MSD Sector 2400's computer for reading the plates.
11. Add MSD Read Buffer T with Surfactant (1X) 150ul/well, read plate immediately in MSD Sector 2400.

B. DETECTION OF HUMAN HGF

1. To a standard MSD streptavidin-coated 96-well plate, add biotinylated capture antibody diluted in 0.5% BSA in Ca^{2+}/Mg^{2+} free PBS at 5 mcg/ml final, 25 mcL/well for 1 hour at RT with shaking.
2. Wash three times with 150 mcL/well Ca^{2+}/Mg^{2+} free PBS.
3. Block with 5% BSA in Ca^{2+}/Mg^{2+} free PBS, 300 mcL/well for 1 hour at RT.
4. Wash three times with 150 mcL/well Ca^{2+}/Mg^{2+} free PBS.
5. Add samples and standards: 100 ul/well for 1 hour at RT with shaking.
6. Wash three times with 150 mcL/well Ca^{2+}/Mg^{2+} free PBS.
7. Add detection antibody diluted in 0.5% BSA in Ca2+/Mg2+ free PBS) 1 ug/ml final, 25 ul/well for 1 hour at RT with shaking.
8. Wash four times with 150 mcL/well Ca^{2+}/Mg^{2+} free PBS.
9. Add MSD Read Buffer T with Surfactant, 150 mcL/well, read plate in MSD Sector 2400.

C. REAGENTS

sMet DETECTION

1. MSD streptavidin-coated 96-well plate catalog no. L15SA-1.

2. Capture antibody: R&D BAF358 biotinylated anti-Met antibody diluted in Ca^{2+}/Mg^{2+} free PBS + 0.5% BSA.
3. Standards: R&D 358-MT purified recombinant human Met ectodomain-Ig fusion protein diluted in Ca^{2+}/Mg^{2+} free PBS + 0.5% BSA.
4. Detection antibody: R&D AF276 anti-Met antibody labeled w/ MSD Sulfotag. Sulfo-tagging is performed per the manufacturer's protocol.
5. MSD Read Buffer T with Surfactant: prepare 20 ml of Read Buffer for 1 plate, using 5 ml of 4X Read Buffer and 15 ml of ultra pure water.

HGF DETECTION

1. MSD streptavidin-coated 96-well plate catalog no. L15SA-1.
2. Capture antibody: R&D Systems MAB694, biotinylated using Pierce EZ-Link Maleimide-PEO Solid Phase Biotinylation Kit, catalog no. 21920.
3. Standards: R&D Systems 294-HG purified recombinant human HGF diluted in 0.5% BSA in Ca2+/Mg2+ free PBS, standard curve covers range from 0.003 ng/ml to 3 ng/ml in semi-log increments.
4. Detection antibody: R&D Systems AF294NA, tagged with MSD Sulfo-Tag NHS Ester, catalog no. R91AN-1, per the manufacturer's protocol.
5. MSD Read Buffer T with Surfactant, catalog no. R92TC-3; 4x.

9.1.6.3 Site Performing the Assay

These studies will be done by the Urologic Oncology Branch, under the direction of Dr. Donald Bottaro.

9.1.7 Met expression in Tissue

All patients will have their tumors analyzed for Met expression by immunohistochemistry (IHC) either with a tumor block, 10 unstained slides or a fresh tumor biopsy. Fresh biopsies, if archival samples are unavailable, will be obtained at baseline from primary tumor sites (bladder) and/or metastatic visceral sites. 4 - 6 core biopsies (or as available) will be taken from a single site.

Please contact trepel@helix.nih.gov, lees@pop.nci.gov, leemin@mail.nih.gov and maria_merino@nih.gov when scheduled and call the Trepel Lab (240) 760 6330 for pickup.

All material will be obtained for review. H&E slides, and one paraffin block or 10 unstained slides will be requested. In house tissue biopsies or resections will be obtained when indicated and tissues process routinely. Immunohistochemistry will be performed. For this procedure, 5-µm, formalin fixed, paraffin-embedded sections will be deparaffinized, and used. Antigen retrieval will be utilized using a microwave oven. Antibodies against c-MET will be used with proper positive and negative controls.

Tissue blocks from outside pathology departments will be stored in the NIH pathology department with attention to Dr. Maria Merino. Unstained slides will be stored by Dr. Andrea Apolo for staining. Biopsies obtained by surgery or interventional radiology will be processed for IHC met staining.

9.1.8 Immune subsets, angiogenesis and other markers in plasma and tissue

9.1.8.1 Collection and Handling

Circulating and intratumoral immune subsets and other markers of the microenvironment, hypoxia-inducible factor (HIF) 1α and 2α and other angiogenesis and/or immunologic markers will be analyzed at 8-18 weeks after treatment.

9.1.8.1.1 Blood

- Blood will be collected in a 6 mL EDTA lavender top tube at baseline and at 8 – 18 weeks after treatment. Blood should only be collected at these timepoints if a tumor biopsy is also performed.
- Please email Jane.Trepel@nih.hhs.gov, lees@pop.nci.gov and leemin@mail.nih.gov 24 hours prior to anticipated collection and call Jane Trepel's lab at 240-760-6330 to arrange for immediate pickup when drawn.

9.1.8.1.2 Tissue

Tissue will be analyzed 8 – 18 weeks after treatment. Any remaining tissue from biopsies obtained on this protocol will also be evaluated. Tissue blocks and slides obtained from outside pathology departments will be analyzed as available. Tissue biopsies, limited to 4 – 6 cores, will be encouraged but done strictly on a voluntary basis. Biopsies will be obtained from primary tumor sites and/or metastatic sites.

9.1.8.2 Processing

Samples will be processed immediately by the Trepel laboratory. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate. The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance. As soon as possible after the patient is scheduled please send email notification to the Trepel lab at trepel@helix.nih.gov, lees@pop.nci.gov and leemin@mail.nih.gov that the biopsy is scheduled. A member of the Trepel Lab will come to the OR/IR suite as soon as the biopsy is available for optimally rapid procurement to maximize tumor viability

9.1.9 Imaging with PET/CT and optional PET/MRI

Patients will undergo a baseline FDG PET/CT of metastatic lesions only along with standard imaging-CT of the chest abdomen and pelvis with or without $Na^{18}F$ PET CT. FDG-PET/CT of metastases will be repeated after 4 (alone) and 8 weeks (along with CT CAP) or until progression

(whichever comes first). The FDG-PET CT will be required, but may be waived at the discretion of the PI. The rationale for an FDG-PET at 4 weeks is that little is known about FDG-PET response to therapy in UC. We believe this is an important potential use of PET given the low objective RECIST response rate in studies in UC. The 8 week scan is taken to assess response to therapy and to assure that we capture progression of disease. The PET will be correlated with standard imaging modality.

Patients will have the option of also undergoing a FDG PET/MR the same day of the PET/CT. PET-MR is a new technology that has recently become available at NIH. Unlike PET-CT, PET-MRI fuses the PET image to an MRI for attenuation correction. In order to explore the value of this technology the patient may be asked whether they are willing to undergo a PET-MRI after completion of their standard PET-CT. After the patient has completed the PET-CT examination, they will be offered additional scanning on a PET-MRI scanner located in the CC/DRD emphasizing that this is optional. No additional injections of radioactivity will be administered and, because the MRI does not utilize ionizing radiation, there will be no additional exposure to the patient. The patient will be escorted to Radiology. The post-injection scan time for PET/MR will be 2 to 2.5 hours. Approximately 1 hour of additional scanning (PET and MR obtained simultaneously) will be performed. Results of the PET-CT and PET-MRI will be compared.

These studies will be done by the Molecular Imaging Program, under the direction of Dr. Peter Choyke.

9.1.10 Comparison of Target Lesion Volume/ Density and RECIST Measurements on CT of Metastatic Urothelial Cancer

We will compare RECIST with semi-automated volume (SAV) / HU measurements, size and attenuation criteria (SACT), mass, attenuation, size and structure (MASS) criteria and Choi criteria in metastatic urothelial lesions. SAV will be measured and standardized utilizing the Lesion Management Application (LMA) of CareStream experimental PACS algorithm. The LMA results will be assessed by two independent radiologists. Differing assessments will be resolved by a third radiologist who will review the results. We will correlate SAV/HU, SACT, MASS and Choi criteria to therapeutic response and determine the practicability of PACS to extract measurement markups that create RECIST reports.

9.1.11 HTG Molecular [1,3,78]

HTG Molecular has a platform to obtain RNA from FFPE tissues and from Paxgene tubes. NCI would send HTG Molecular paired coded samples of pre treatment and post treatment Paxgene samples and FFPE slides (H&E and serial unstained slides) for analysis.

In this study, we will access the performance of the HTG EdgeSeq Immuno-Oncology Assay and OBP Assays on 20 trial cases with both pre and post treatment samples. Each case will have FFPE tissue and matched PaxGene samples to be assessed. A small number of additional samples corresponding to atypical histologies and MET lesions will also be analyzed in parallel as additional data points and controls.

Our priority is to demonstrate the performance of FFPE and Paxgene samples for further utilization in clinical trials and secondary to determine if pathway and immune expression biomarkers are differentially expressed between pre and post treated samples.

9.1.11.1 Processing at HTG:

Lysates:

- Lysis method. Sample lysis shall be performed in accordance to OP-00034, HTG EdgeSeq Processing.
- Sample input volumes for each sample type: Cells = 20,000/well, FFPE = 5mm2/well
- Unstained slides to be macro-dissected per NIH pathology recommendations, focusing on tumoral and peritumoral regions.
- Lysates shall be aliquoted into several tubes so in order to minimize freeze/thaw cycles throughout the experiment and store sample for further analysis via OBP, IO assays and if required re-runs.

Specimens, data or information will be coded so that the provider of the samples/data can link them to specific individuals but the receiver will not be able to do so.

Coded samples will be sent under an MTA to:
TG Molecular Diagnostics, Inc.
Attention:
Mark Stern, Ph.D.
Vice President, Head of Immuno-Oncology Franchise
HTG Molecular Diagnostics
3430 E Global Loop
Tucson, AZ 85706
C: (848) 213-5051
T: (877) 289-2615
F: (520) 547-2837

9.1.12 Xenobiotic Metabolism

Previously we have identified the role of hypermethylation in decreasing the expression of cytochromes P450 1A1 (CYP1A1) and P450 1B1 (CYP1B1) in tumors compared to matched benign tissues. Furthermore, using a data mining approach on the TCGA data, we have recently uncovered yet another enzyme involved in xenobiotic metabolism, aldehyde oxidase (AOX1), as being progressively down-regulated during progression of bladder cancer through various clinical stages (T2-T4). AOX1 is known to play an essential role in amino acid synthesis and xenobiotic metabolism and metabolizes N-heterocycles and nitrosamines, azo dyes or nitropolycyclic aromatic hydrocarbons, many of which are known to increase the risk for bladder cancer. Importantly, using Tissue Microarrays on 190 BCa patients we confirmed a loss of AOX1 protein expression in advanced stages of bladder cancer. Based on all of the above data, we hypothesize that xenobiotic metabolism plays a key role in bladder cancer progression, its enzymes like AOX1 regulate tumor progression and xenobiotic metabolites could function as non-invasive markers to monitor tumor progression. Our aims include:

- Define stage-specific profiles of key xenobiotic metabolites in bladder cancer plasma samples.
- Develop a first-generation multiplex panel of tissue-derived xenobiotic metabolites in plasma that correlates with clinical staging of the disease.

Other aims included

- Identify race specific metabolic markers in bladder cancer plasma.
- Identify a metabolic signature for the bladder cancer smoker

9.1.12.1 Sample Processing

Plasma - 100 uL

Please aliquot in Eppendorf tube – Prefer not to have EDTA. Please store in -80 and ship on dry ice.

Specimens, data or information will be coded so that the provider of the samples/data can link them to specific individuals but the receiver will not be able to do so.

Shipping:

Nagireddy Putluri, Ph.D
Associate Professor
120D, Jewish Building
One Baylor Plaza, Houston, TX, 77030

9.2 CORRELATIVE STUDIES

9.2.1 Quality of Life Questionnaire

Patients will be asked to complete the MDA Anderson Symptom Inventory (MDASI) Core items (See **Appendix G**) in order to assess their symptoms. Surveys will be completed at baseline and on day 1 (± 5 days) of cycle 3 of cabozantinib. Each survey should take about 5 – 10 minutes to complete.

9.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered and tracked in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

9.3.1 Blood Processing Core (BPC)

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be bar-coded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts.

Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number; time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample Storage and Destruction

Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20° or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Saliva samples will be stored at room temperature. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

9.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

9.4.1 Saliva

9.4.1.1 Collection and handling

- 3 mL of saliva will be collected using the Oragene saliva collection kit (DNA Genotek). The sample may be collected at any time after informed consent has been obtained, but collection is preferred at baseline.
- Ideally, the patient should be advised not to eat or drink anything 30 minutes prior to collection.
- Once the sample is obtained, the top of the device is closed, releasing a preservative, the top is removed and a cap is placed on the tube.

- The date and exact time of the collection should be recorded on the sample.
- Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for immediate pick-up.

9.4.1.2 Handling

As described in section **9.3**, samples will be relabeled with barcoded labels generated by LABrador on arrival in the Figg Lab.

9.4.1.3 Site performing the analysis

Genetic/genomic studies will be performed in the laboratory of Michael Dean, Ph.D., CCR, NCI.

9.4.2 Tumor Biopsy

9.4.2.1 Collection and handling

- Biopsy material remaining from either the baseline collection (see section **9.1.7**) or the collection at 8 – 18 weeks (see section **9.1.8**) should be placed on ice or frozen as soon as possible after collection.

  In the case that there is limited biopsy material, tissue distribution should be prioritized as follows:

  1. Analysis of met expression (Dr. Maria Merino)
  2. HGF and cabozantinib target analysis (Dr. Donald Bottaro)
  3. Immune subset analysis (Jane Trepel)
  4. Genetic/Genomic Analysis (Dr. Michael Dean)
  5. HTG Analysis (Dr. Stern)

9.4.2.2 Processing

The sample will be processed in the Trepel lab as described in section **9.1.8.2**. DNA will be extracted from leftover tissue per Trepel lab procedures and will be assigned a unique barcode that can be linked to the original specimen collected, annotated with clinical information. The DNA extracted from the samples will be sent to the Dean lab for analysis.

9.4.2.3 Site performing the analysis

Genetic/genomic studies will be performed in the laboratory of Michael Dean, Ph.D., CCR, NCI and HTG Molecular as per section **9.1.11**.

9.4.2.4 Shipping

Extracted DNA from biopsies should be sent to:

Julie Sawitzke
Center for Cancer Research, NCI
Building 560, Room 21-43
Frederick, MD 21702
Phone: 301 845 1997
Email: sawitzkej@mail.nih.gov

9.4.3 Scope of analysis

Tumor samples will be used as a source of DNA for genetic/genomic studies. Saliva samples will be used as a source of genomic (germline DNA) from the patients to compare with tumor DNA

for somatic mutations. Whole genome and whole exome studies may be conducted using the material collected. Studies for the analysis of chromosomal abnormalities may also be performed.

9.4.4 Confidentiality of medical information/biological specimens

Samples will be labeled with unique identifiers generated in the Figg or Trepel labs respectively and transferred to the Dean lab for analysis. No patient identifiers (e.g., medical record number, patient name or initials) will be included with the sample. Dr. Dean's lab will create a separate unique sample ID using Labmatrix that can be linked to the clinically annotated identifiers from the source labs. Samples will be stored in coded, locked freezers in a room that is locked when unoccupied. The storage facility is located in a building that is key card secured. Raw and analyzed sequencing data will be stored on dedicated server and on a hard drive in the investigator's locked office. Analyzed data will also be uploaded into the secure Labmatrix database.

Only the PI and study personnel who interact directly with the patients will have access to patient records which include personally identifiable information. Investigators conducting the individual sample testing will only have access to coded identification numbers and coded patient information (i.e. treatment regimens, treatment responses, diagnoses, pathology information).

No personally identifiable information will be released to third parties and samples and data will only be shared with other researchers with the permission of the IRB and under the proper Material Transfer Agreements.

Sometimes, because a group collaboration or journal policy requires it, a subject's genetic data may be deposited in a database such as dbGaP. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

9.4.4.1 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

9.4.5 Management of Results

In the unlikely event that clinically actionable incidental findings are discovered, living patients will be contacted and asked if they would like to submit a blood sample to be tested at a CLIA certified lab and meet with a certified genetic health care provider to discuss the implications of this type of testing. Patients will be offered the option for a legal next of kin to be contacted if they are deceased at the time of the research finding. The legal next of kin would be offered genetic counseling that would include the distinction between a clinical and research finding and would be offered the opportunity to have those findings confirmed in a living relative of the patient.

Note: Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current

guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

Incidental findings will only be reported to the patient within the first 5 years of signing the consent.

9.4.6 Genetic Counseling

Should any significant incidental findings be discovered, genetic counseling will be provided on a consultation basis by the NHGRI, NIH. Any genetic counseling or testing at a CLIA certified lab will be funded by the Center for Cancer Research at the time of the event (s).

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated.

Procedure	**Study Treatment Period**			***Post-Treatment Period***	
	Within 28 days prior to 1st Dose of Study Treatment	**Within 1 week prior to the first dose of Study Treatment**	**Day 1 of Weeks 3, 5, 7, 9, 11, 13, and 15 then every 4 weeks (± 7 days)**	**30 - 37 Days after last dose**	**Long Term Follow Up[9]**
Informed consent	X				
Demographics	X				
Medical and cancer history/demographics	X				
Dental examination (baseline)[1]	X				
24 hour urine collection if needed (see section **3.1.1.13**)	X				
Physical examination	X	X	X		
Height	X				
Weight	X	X	X		
Vital signs	X	X	X		
ECOG performance status	X	X	X		
Clinical laboratory tests[2]	X	X	X		
Urinalysis (including UPCR)	X	X	X		

Procedure	**Study Treatment Period**			***Post-Treatment Period***	
	Within 28 days prior to 1st Dose of Study Treatment	**Within 1 week prior to the first dose of Study Treatment**	**Day 1 of Weeks 3, 5, 7, 9, 11, 13, and 15 then every 4 weeks (± 7 days)**	**30 - 37 Days after last dose**	**Long Term Follow Up[9]**
PT/INR, PTT	X	X	X[3]		
TFTs	X	X	X[3]		
12-lead ECG[4]	X	X	X[3]		
Cabozantinib administration			X (daily)		
Pregnancy test (in women of childbearing potential)	X	X	X[3]		
Tumor assessment: CT CAP or MRI scan ± NaF PET CT [5]	X		X (every 8 weeks)[11]		
Concomitant medications			X		
Investigational FDG PET/CT[8]	X		X (weeks 4, 8)		
Research blood, saliva and urine	X[6]		X[6]		
Biopsy/archival tissue obtained[7]	X		X (optional, week 8 – 18)		
QOL Assessment[10]	X		X (week 9 only)		
Adverse events		Continuous			
Follow-up phone call				X	X

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; UPCR, urine protein/urine creatinine ratio

[1] Dental examination required at baseline in patients that have been treated with or are currently taking bisphosphonates

[2] Clinical laboratory tests include: a standard hematology panel (CBC, differential, platelets) and chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase (GGT), glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein). Refer to section **5.3.4**)

[3] Every 4 weeks

[4] Three ECGs should be obtained within 30 minutes but at least 2 minutes apart if there is an increase in QTc to an absolute value > 500 msec using the Fridericia correction formula. See section **5.3.1**

[5] All sites of known disease must be assessed. Baseline scans must be repeated if patient is off of study drug for > 6 weeks.

[6] Please see section 9 or **Appendix F** for research blood and urine collection

[7] Please see sections **9.1.7**, **9.1.8.1.2** **and** **9.4.2** or **Appendix F** for biopsy or archival tissue specifications

[8] Performed on patients with metastatic disease. See section **9.1.9**.

[9] Will attempt patient contact every 2 months after 30 – 37 day phone call to determine survival status

[10] QOL assessments will be performed at baseline and after cycle 3 of cabozantinib. Please see section **9.2.1** for further details.

[11] Patients who are off treatment due to complete response after 3 years will have their assessments every 12 weeks.

11 MEASUREMENT OF EFFECT

11.1 ANTITUMOR EFFECT – SOLID TUMORS

Patients with measurable disease will be assessed primarily by CT scan of the chest, abdomen and pelvis. MRI may be used in subjects unable to tolerate contrast. For the purposes of this study, patients should be re-evaluated every 8 weeks.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [*Eur J Ca* 45:228-247, 2009] and Prostate Cancer Clinical Trials Working Group criteria (PCWG2)[79]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study agents.

Evaluable for objective response. All of the patients who met the eligibility criteria and who have received at least 8 weeks of therapy are evaluable for response. Patients that have: progressive disease, early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (not assessable, insufficient data) should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray or as $\geq$10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater

than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PETWhile FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

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

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

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one

	or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Metastatic bone lesions

Two new bone lesions on $Na^{18}F$ PET CT that is associated with characteristic bone changes on CT will be defined as progressive disease (PD).[79] $Na^{18}F$ uptake changes including changes in SUV or flares of known lesions will not be counted as PD. Only new lesions with associated CT changes will be counted as PD.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

** Only for non-randomized trials with response as primary endpoint.

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease or death is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12 DATA COLLECTION / DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 0 (Adverse Events: List and Reporting Requirements).

12.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system NCI CCR C3D database within 14 days of collection and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for a minimum of 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g.: laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)
- Toxicity was assessed according to protocol (laboratory report slips, etc.)
- Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

12.2 GENOMIC DATA SHARING PLAN

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

12.3 DATA REPORTING

12.3.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. The C3D data management system will be used to capture data and report to the clinical data update system

(CDUS). Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.4 CTEP MULTICENTER GUIDELINES

N/A

12.5 COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-

Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.6 Material Transfer Agreement (MTA) for Samples Sent to HTG Molecular

An MTA is to be filed for samples to be sent to HTG Molecular as outlined in section **9.1.11**.

12.7 MTA for Samples Sent to Baylor College

An MTA for samples to be sent to Nagireddy Putluri Ph.D at Baylor College as outlined in section **9.1.12**, will be finalized upon approval of the amendment O dated 11/08/2017.

13 STATISTICAL CONSIDERATIONS

13.1 STUDY DESIGN/ENDPOINTS

The primary objective of this study is to determine if patients with advanced or metastatic bladder cancer will exhibit responses to XL184.

The study will be conducted as an optimal two-stage phase II trial (Simon R, Controlled Clinical Trials 10:1-10, 1989), in order to rule out an unacceptably low 5% overall response rate (ORR; p0=0.05), in favor of a modest response rate of 20% (p1=0.20). With alpha=0.05 (probability of accepting a poor treatment=0.05) and beta = 0.10 (probability of rejecting a good treatment=0.10), the study will initially enroll 21 evaluable patients and if 0 to 1 of the 21 have a response by RECIST version 1.1, then no further patients will be accrued. If 2 or more the first 21 have a response, then accrual would continue until a total of 41 patients have enrolled. As it may take several weeks to determine if a patient has experienced a response, a temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 2 to 4 responses in 41 patients, this would be an uninterestingly low response rate, while if there were 5 or more responses in 41patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 72%.

Patients with bone-only disease will be accrued and evaluated separately from all other patients, as they cannot be evaluated with the same methods or same degree of accuracy as all other patients with this disease. It is expected that only 15-20% of all patients enrolling on the trial will have bone-only disease. The patients which would be expected to enroll while awaiting enrollment of the main set of 41 patients will be considered a hypothesis generating cohort to determine if any patients show some evidence of avoiding worsening disease while receiving XL184. They will be evaluated using $Na^{18}F$ PET CT scans in addition to standard CT CAP (or MRI) and FDG PET and will be considered to have favorable results if additional lesions are not noted compared to baseline. As this is a small set of patients, the results will be used to determine if a more definitive subsequent study in these patients would be warranted.

Patients with non transitional cell carcinoma will be accrued and evaluated separately from all other patients. Because no data for an expected response rate for comparison currently exist with regard to this group of patients, this will be an exploratory study. The patients which would be expected to enroll while awaiting enrollment of the main set of 41 patients will be considered a hypothesis generating cohort to determine if any patients show some evidence of avoiding worsening disease while receiving XL184. They will be evaluated using standard CT CAP (or MRI) and FDG PET and will be considered to have favorable results if additional lesions are not noted compared to baseline. As this is a small set of patients, the results will be used to determine if a more definitive subsequent study in these patients would be warranted.

13.2 SAMPLE SIZE/ACCRUAL RATE

In order to allow for up to 41 evaluable patients plus up to 21 patients with either bone only or non TCC bladder, urethra, ureter, or renal pelvis cancer who will be evaluated in separate cohorts, the accrual ceiling will be 71 patients. This will allow enrollment of up to 8-9 patients who may be considered inevaluable. It is anticipated that 2-3 patients per month may enroll on this trial; thus,

2 to 3 years is anticipated as the accrual period for this study. Subjects will be accrued into the exploratory cohorts (cohorts 2 and 3) for only as long as subjects are being accrued onto the hypothesis generating cohort (cohort 1).

13.3 STRATIFICATION FACTORS

N/A

13.4 ANALYSIS OF SECONDARY ENDPOINTS

The secondary endpoint of progression free survival and survival will also be analyzed via a Kaplan-Meier curve. This latter, secondary, evaluation will be based on all patients who are able to be assessed in either the first (retrospectively) or second stage of accrual. The secondary endpoint of the assessment of non RECIST imaging criteria and association with treatment response (RECIST) will be analyzed via appropriate non-parametric methods, such as a Wilcoxon rank sum test to compare parameters between responders and non-responders.

Toxicity and safety are also a primary consideration for use of this agent in this population. The worst grade of each type of toxicity noted per patient will be tabulated and reported according to the NCI Common Toxicity Criteria, version 4.0.

Evaluations of any laboratory and correlative parameters obtained will be done using exploratory techniques. Comparisons of parameters between patients who do and do not respond to therapy will be done using non-parametric methods such as a Wilcoxon rank sum test. The results will be reported without any formal adjustment for multiple comparisons.

For the secondary objective of FDG PET scan evaluation we will examine the change of uptake of FDG over time and explore its relationship with response to therapy. Descriptive statistics such as percent changes of FDG over time and its overall trend in relation to the clinical endpoints will be reported. The data obtained from this study will be used for hypothesis generating and sample size planning for the main study.

13.5 REPORTING AND EXCLUSIONS

13.5.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with cabozantinib.

13.5.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in

exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14 HUMAN SUBJECTS PROTECTIONS

14.1 RATIONALE FOR SUBJECT SELECTION

Subjects with progressive urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis will be eligible for participation in this study. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

14.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have urothelial cancer, and because of unknown toxicities of this agent in the pediatric patient.

14.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **14.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.4 Evaluation of Benefits and Risks/Discomforts

14.4.1 Benefits

The potential benefit to a patient on this study is a reduction in the bulk of their tumor and improvement in cancer lesions, which may or may not have favorable impact on symptoms and/or survival.

14.4.2 Risks

Radiation Risks

Undergoing the research FDG PET CT scans will cause subjects to be exposed to approximately 3.2 rem which is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

Other Risks

Additional risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of cabozantinib.

14.5 Risks/Benefits Analysis

Although urothelial cancer is a chemosensitive malignancy with response proportions of over 50% with conventional cytotoxic regimens, the response durations are short and the median survival of patients with metastatic disease is approximately 14 months. There is no FDA-approved second line drug for metastatic urothelial cancer. Inhibition of angiogenesis has demonstrated antitumor efficacy in patients with metastatic UC. Cabozantinib inhibits multiple receptor kinases with growth promoting and angiogenic properties, including MET and VEGF, which are known to be over-expressed in bladder cancer.

The use of cabozantinib as a second line agent in metastatic urothelial cancer has the potential to improve outcomes in this patient population. Given the efforts to minimize risk with the administration of this combination, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects.

14.6 Consent and Assent Process and Documentation

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

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

It will be documented on the case report form that informed consent has been obtained.

14.6.1 Telephone re-consent

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented in the medical record.

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16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

16.2 APPENDIX B: PATIENT INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

*The patient _____ is enrolled on a clinical trial using the experimental **cabozantinib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Cabozantinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Cabozantinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is **CYP3A4**. This enzyme breaks down cabozantinib, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. Cabozantinib must be used very carefully with these medicines, or you may need to switch to alternate medications.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/ or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit or Seville orange: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking cabozantinib
    - For indigestion, take antacid at least 2 hours (preferably 4 hours) after taking cabozantinib and at least 14 hours before the next dose of cabozantinib if possible. Avoid using ranitidine, famotidine, omeprazole, lansoprazole, rabeprazole, pantoprazole, or esomeprazole. If antacids are not adequate, please contact the research team member before taking any other medications.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is **Dr. Andrea Apolo** and she can be contacted at **301-480-0536**.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	**INFORMATION ON POSSIBLE DRUG INTERACTIONS**
You are enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib).** This clinical trial is sponsored by the NCI. **XL184 (cabozantinib)** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	You are enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib).** This clinical trial is sponsored by the NCI. **XL184 (cabozantinib)** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

16.3 APPENDIX C: PATIENT MEDICATION DIARY

Cycle #_____

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each Cycle.
2. You will take ___ cabozantinib pills once each day.
3. Record the date, the number of pills you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottles and this form to your physician when you go for your next appointment.

Date	**Day**	**Cabozantinib** (taken once a day)		
		# pills, when taken	**# pills missed**	**Comments**
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			

Patient's Signature: _____ Date: _____

16.4 APPENDIX D: CCR PATIENT SELF-ADMINISTERED STUDY AGENT COMPLIANCE LOG

This form is to be updated at every study contact where patient receives or returns study drug. This form may be used for multiple self-administered study agents. This form is to be used in conjunction with a note in CRIS about study drug self-administration and case report form and will be maintained in the research record. If patient is bringing back their study drug and you will not be returning that to the pharmacy, rather, the patient will be taking it back home with them, please use the form entitled '*CCR Patient Self-Administered Study Agent Interim Compliance Form'*.

CC Protocol Number:_____ Principal Investigator:_____

Protocol Title:_____

Patient's Medical Record Number:_____ Patient's Name:_____

Patient Study ID: _____ Cycle Number_____

Date Dispensed	**Amount Dispensed**	**Dose Form** *(e.g., tablets, pills, bottles, capsules, vials)*	**Date Returned**	**Actual Amount Returned**	**Expected Amount Taken**	**Expected Amount Returned**	**Reason for difference between actual and expected amount returned, if applicable**	**Site Staff Initials**
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					
____/_____/20_____			____/_____/20_____					

Date Dispensed	**Amount Dispensed**	**Dose Form** *(e.g., tablets, pills, bottles, capsules, vials)*	**Date Returned**	**Actual Amount Returned**	**Expected Amount Taken**	**Expected Amount Returned**	**Reason for difference between actual and expected amount returned, if applicable**	**Site Staff Initials**
(mm/dd/yyyy)			(mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20_____ (mm/dd/yyyy)					

16.5 APPENDIX E: BLOOD PRESSURE MONITORING FORM

For use in patients with a history of hypertension

Instructions 1. Take your blood pressure once per week during each cycle of cabozantinib 2. Record the date you took your blood pressure and your blood pressure below 3. Bring this form with you at your next study visit		
Week	**Date**	**Blood Pressure**
1	_____	_____/_____
2	_____	_____/_____
3	_____	_____/_____
4	_____	_____/_____

16.6 APPENDIX F: SAMPLE COLLECTION FOR CORRELATIVE STUDIES

Test description	Amount/Type/Tube/Handling	Collection Timing	Contact	Special Instructions
Saliva	Oragene saliva collection kits (DNA Genotek)	At any time after consent is signed, but preferably at baseline	Please email NCIBloodcore@mail.nih.gov 24 hours prior to anticipated collection and page 102-11964 for pickup.	store at room temp
Met expression in tissue	4-6 cores, Tumor block, 10 unstained slides, or a fresh tumor biopsy	Pre-treatment	When scheduled email Jane Trepel (trepel@helix.nih.gov), Sunmin Lee (lees@pop.nci.gov), Mi-Jung (leemin@mail.nih.gov, and Maria Merino When patient arrives at IR call Jane Trepel (240) 760-6330 and Maria Merino	Analyzed by immunohistochemistry and flow cytometry as appropriate Tissue biopsies strictly on voluntary basis
HTG EdgeSeq Immuno-Oncology and OBP Assays	H&E and serial unstained slides		HTG Molecular Diagnostics, Inc. 3430 E. Global Loop Tucson, AZ 85706 T: (877) 289-2615 F: (520) 547-2837	
CEC, CEP, and CTC	Two 10cc Lavender top EDTA tube Three 8mL blue-tiger top BD Vacutainer Preparation tube with sodium citrate	Pre-treatment	When scheduled email Jane Trepel (trepel@helix.nih.gov), Sunmin Lee (lees@pop.nci.gov), Mi-Jung (leemin@mail.nih.gov)	Gently invert sample several times immediately after collection, store at room temp
	Date and Time tube	C3D1	When drawn call Trepel lab (240) 760-6330 for immediate pick up	
C-Met analysis by real-time RT-PCR	PAXgene tube (PreAnalytix; 2.5cc blood per tube)	Pre-treatment	When scheduled email Jane Trepel (trepel@helix.nih.gov), Sunmin Lee (lees@pop.nci.gov), Mi-Jung (leemin@mail.nih.gov)	invert several times and place at room temp or refrigerate
	Date and Time tube	C3D1	When drawn call Trepel lab (240) 760-6330 for immediate pick up	
IL-8 circulating cytokine levels	One 5mL red top tube	C1D1, C1D15, C2D1	When scheduled, email Jane Trepel (trepel@helix.nih.gov), Sunmin Lee (lees@pop.nci.nih.gov), Min-Jung Lee (leemin@mail.nih.gov)	store at room temp

Test description	Amount/Type/Tube/Handling	Collection Timing	Contact	Special Instructions
	Date and Time tube		When drawn call (240) 760-6330 (Trepel lab) for immediate pick up	
Genetic biomarkers (VEGFR2)	One 10mL EDTA lavender top tube	C2D1	e-mail 24 hr prior, Please page 102-11964 - Figg lab	Invert 8-10 times, place on wet ice and store at 4°C in refrigerator until procession
	Date and Time tube			
Angiogenesis markers	4mL EDTA tube	C1D1, C1D15, C2D1, progression	E-mail 24hr prior, Please page 102-11964 - Figg lab	Invert EDTA tube 2-4 times, place on wet ice and store at 4°C in the refrigerator until processing for a maximum of 30-60 min.
	Date and Time tube			
Plasma HGF and MET	One 3mL EDTA tube	prior to treatment, every visit	Email 24 hr prior, Please page 102-11964 - Figg lab	Should be centrifuged within 30 min
	Date and Time tube			Refrigerate samples
Analysis of tissue HGF and cabozantinib targets	4-6 cores of fresh tumor biopsy	• Pre-treatment • 8 – 18 weeks	When scheduled, contact Dr. Bottaro to notify of biopsy date and time (301-402-6499) and to arrange for pick up of sample during biopsy	The interval between sample acquisition and freezing on dry ice must not exceed 2 minutes. Tissue biopsies strictly on voluntary basis
Urinary MET and urine spot creatinine	Collect at least 2mL of urine	prior to treatment, every visit	Email 24 hr prior, Please page 102-11964 - Figg lab	Note urine source: void, percutaneous stent, Foley, neobladder, Indian pouch, or ileal conduit

Test description	Amount/Type/Tube/Handling Date, Time and source of urine on tube	Collection Timing	Contact	Special Instructions
Immune subsets and angiogenesis markers in tissue	4-6 cores of fresh tumor biopsy	8-18 weeks post treatment	When scheduled email Jane Trepel (trepel@helix.nih.gov), Sunmin Lee (lees@pop.nci.gov), Mi-Jung (leemin@mail.nih.gov), and Maria Merino	Tissue biopsies strictly on voluntary basis
Xenobiotic Metabolism	100 ul of plasma		Nagireddy Putluri, Ph.D Associate Professor 120D, Jewish Building One Baylor Plaza, Houston, TX, 77030	Eppendorf tube

16.7 APPENDIX G: MDASI QUALITY OF LIFE ASSESSMENT

Date: _____ **Institution:** _____

Subject Initials: _____ **Hospital Chart #:** _____

Study Subject #: _____

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: _____ **Institution:** _____

Subject Initials: _____ **Hospital Chart #:** _____

Study Subject #: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interefered Completely 10
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○