TITLE: A Phase 2 Study of Cabozantinib (XL184), a Dual Inhibitor of MET and VEGFR, in Patients with Metastatic Refractory Soft Tissue Sarcoma

Abbreviated Title: Ph2 Cabozantinib Soft Tissue Sarcoma

Coordinating Center: Developmental Therapeutics Clinic (NCIDTC)
National Cancer Institute
10 Center Drive
Bethesda, MD 20892

Participating Sites: City of Hope
Stanford University School of Medicine
University of Southern California

Principal Investigator: A. P. Chen, MD[A-E]
Center Drive Bldg 31 Rm 3A44
Bethesda, MD 20892
Phone: (240) 781-3320; Fax: (301) 402-0172
chenali@mail.nih.gov

Statistician: Larry Rubinstein, PhD, BRB/DCTD[E]
9609 Medical Center Dr, Room 5W106
Phone: (240) 276-6026
rubinsteinl@mail.nih.gov

Research Nurse: Ashley Bruns, RN, DCTD/NIH[A,B,E]
10 Center Drive, Bldg 10/Rm 8D53
Bethesda, MD 20892
Telephone: (240) 858-3162
Fax: (301) 451-5625
ashley.bruns@nih.gov

California Cancer Consortium (CCC) Participating Sites:

City of Hope (CoH): FWA # FWA00000692 IRB: David Holt Director, Clinical Research Protections City of Hope IRB of Record: City of Hope Natl Med Ctr & the Beckman Rsch Inst IRB#1 IRB IORG#: IORG0000042	Principal Investigator: Mark Agulnik, MD, FACP City of Hope Medical Center 1500 E. Duarte Rd. Duarte, CA 91010 Phone: 626-218-9200 Fax: 626-218-8233 magulnik@coh.org Pharmacy: Oscar Martin, PharmD Investigational Drug Service, City of Hope

1500 E. Duarte Rd, Duarte, CA 91010 Phone: (626) 218-3099; E-mail: daholt@coh.org	1500 E. Duarte Rd., Duarte, CA 91010 Phone (626) 256-4673 x62398; Fax: (626) 930-5378 E-mail: omartin@coh.org
University of Southern California (USC): FWA #00005906 IRB Director: Sandy Jean University of Southern California Health Sciences Institutional Review Board IRB IORG# IRB00000484 LAC+USC Medical Center General Hospital Suite 4700 1200 North State St. Los Angeles, CA 90033 Phone: (323) 276-2231 Sandy.Jean@med.usc.edu	Principal Investigator: James Hu, MD University of Southern California 1441 Eastlake Ave. Los Angeles CA. 90033 Phone: 323-865-0813 Fax: 323-865-0061 jameshu@med.usc.edu USC Pharmacy Contact: Charlene Chiu, PharmD USC/Norris Comprehensive Cancer Center / Investigational Drug Services 1441 Eastlake Avenue, Rm. 2407 Los Angeles, CA. 90033 Phone: (323) 865-3538; Fax: (323) 865-0857 IDSPharmacy@med.usc.edu
Stanford University School of Medicine FWA00000935 Stanford University Administrative Panel on Human Subject in Medical Research IORG #0000208 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306 Pharmacy contact: Martha "Marty" Hamilton Stanford Hospital and Clinics Investigational Pharmacy 300 Pasteur Drive, Room H0302 Stanford, CA 94305 Phone (650-725-5295) Fax #: 650-725-6262 MaHamilton@stanfordhealthcare.org	Principle Investigator: Shivaani Kummar, MD Stanford University School of Medicine 780 Welch Road, Rm CJ250L Palo Alto, CA 94304 (650) 724-9084 skummar@stanford.edu Kristine M. McGlennen, MN, RN Cancer Clinical Trials Office 800 Welch Rd., FC2C19 Stanford, California 94305 Tel: (650) 723-3589 / Pager: (650) 723-8222 ext. 26827 /Fax: (650) 736-8092

CTEP Monitor: John J. Wright, MD, PhD

NCI Supplied Agent: Cabozantinib (NSC 761968)

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Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- Soft tissue sarcomas (STS) are a relatively rare heterogeneous group of tumors that constitute about 1% of adult cancers.
- The mainstay of treatment for advanced disease has been palliative chemotherapy with a median overall survival of approximately 12 months. This has not changed considerably in the past years and there is an unmet need for newer targeted therapies.
- VEGF levels are elevated in patients with STS and various sarcoma cell lines express high levels of activated c-Met receptor.
- We hypothesize that dual targeting of the VEGF and c-MET pathways with cabozantinib would result in clinical benefit in patients with soft tissue sarcoma.

Objectives:

Primary:

- Assess the response rate (CR+PR) of cabozantinib in patients with soft tissue sarcomas.
- Assess the 6 month progression free survival (PFS) of cabozantinib in soft tissue sarcomas.

Secondary:

- Determine and compare circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of cabozantinib.

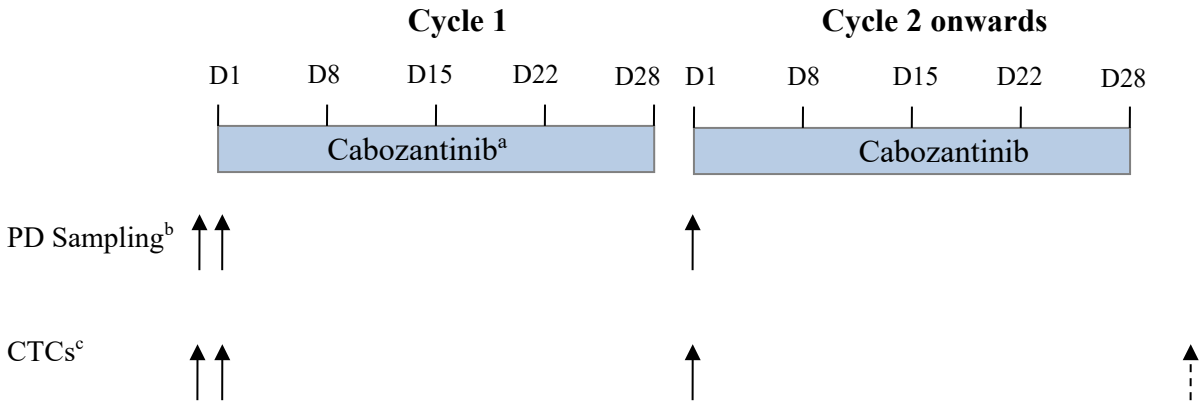
Eligibility:

- Patients must have had disease progression following one line of standard therapy
- Age ≥ 18 years.
- Adequate organ function.
- Patients will be stratified based on prior VEGFR TKI therapy.

Design:

- All patients will receive cabozantinib at 60 mg PO daily in 4 week cycles.
- Tumor response evaluations by imaging will be done every 2 cycles (less frequently for patients on study more than one year).
- The study will be conducted as a dual-endpoint two-stage Phase II trial to target objective tumor response rate (CR+PR) of 30% against an unacceptably low rate of 10%, and 6-month PFS rate of 65% against an unacceptably low rate of 45% (corresponding to median PFS of 9.6 vs. 5.2 months).
- The trial will accrue up to 50 evaluable patients.

SCHEMA



[a]Cabozantinib 60 mg po q day continuously throughout. Cabozantinib will be taken on an empty stomach 1 hour before, or 2 hours after, a meal.

[b]Blood samples for PD analyses (mandatory at the NCI but optional at participating sites) collected at baseline (pre-treatment), on C1D1 (3-6 hours post dose), and on C2D1 (3-6 hours post dose).

[c]Blood samples for CTC analyses (optional) collected at baseline (pre-treatment), on C1D1 4 hours (+/- 1 hour) post dose, on day 1 of all subsequent cycles before drug administration, and at disease progression.

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1 OBJECTIVES

1.1 Primary Objectives

- Assess the response rate (CR+PR) of cabozantinib in patients with soft tissue sarcomas.
- Assess the 6 month progression free survival (PFS) of cabozantinib in soft tissue sarcomas.

1.2 Secondary Objectives

- Determine and compare circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of cabozantinib.

2 BACKGROUND

2.1 Soft Tissue Sarcoma (STS)

Soft tissue sarcomas (STS) are a relatively rare heterogeneous group of tumors that arise mainly from embryonic mesoderm. They constitute about 1% of adult cancers with 10,000 new cases diagnosed every year in the US with an overall mortality rate of 3,920 cases per year including adults and children.[1] More than 50 different histological types have been identified the most common of which are pleiomorphic sarcoma also known as malignant fibrous histiocytoma (MFH), GIST, liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumors.[2] Diagnosis at an early stage is crucial since complete surgical resection yields the best prognosis. However, the lack of a screening modality makes it difficult with more than 50% of patients developing metastasis during their course of disease decreasing their 5 yr survival to below 10%.The mainstay of treatment for the advanced disease patients has been palliative chemotherapy. The chemotherapy backbone of an anthracycline with or without ifosfamide has been used for decades and yielded response rates of 20-30% and a median overall survival of approximately 12 months.[3-10] Anthracycline resistant STS and certain subtypes like leiomyosarcoma appear to have better responses to the combination of gemcitabine and docetaxel which is the only regimen in STS which has demonstrated an overall survival advantage in the phase III randomized setting.[11-13] With the median survival of these patients having changed very little over the past decade there is an unmet need for newer targeted therapies.

One of the targets that have emerged in this setting is the tumor produced angiogenic factor vascular endothelial growth factor (VEGF). It has been shown that VEGF levels are elevated in patients with STS and correlates with the grade of the tumor.[14-17] Factors other than VEGF, such as platelet-derived growth factor (PDGF), are also likely to be involved in STS angiogenesis.[18] Bevacizumab a monoclonal antibody against VEGF has been studied in combination with chemotherapy regimens including gemcitabine, docetaxel[19] and temozolomide[20] with promising results. Pazopanib, an oral angiogenesis inhibitor that targets VEGF receptors (VEGFRs), PDGF receptors (PDGFRs), and c-kit has also been studied in STS in phase II[21] and III settings[22] to show improvement in PFS by 13 weeks compared to placebo.

Hepatocyte growth factor/scatter factor (HGF/SF) activates the c-Met receptor tyrosine kinase and promotes cell proliferation, survival, and invasion and also plays a role in angiogenesis.[23,24] Various sarcoma cell lines express high levels of activated c-Met receptor and suggesting that HGF/SF signaling pathway may contribute to sarcomagenesis.[25] Interruption of autocrine or paracrine HGF/SF c-met signaling with the monoclonal antibody AMG102 in leiomyosarcoma cell line SK-LMS-1 and in mouse xenograft models has shown significant antitumor effect.[26] It has also been shown that clear cell sarcoma cells are dependent on HGF/C-Met axis[27] for invasion, chemotaxis, and survival.

2.2 Cabozantinib (XL184)

Cabozantinib is a new chemical entity that inhibits the receptor tyrosine kinases MET (hepatocyte growth factor [HGF] receptor) and VEGFR2 (vascular endothelial growth factor receptor 2). Both MET and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and MET is particularly associated with tumor invasiveness and metastasis. In vivo pharmacodynamic activity of cabozantinib against MET and VEGFR2 has been demonstrated in both preclinical and clinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis, tumor invasiveness and metastasis, and the progression of tumors in bone. Cabozantinib inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2011). The primary targets of cabozantinib are MET and VEGFR2; additional targets include RET, AXL, KIT, and TIE-2.

Cabozantinib is a potent inhibitor of MET and VEGFR2 with half-maximal inhibitory concentration (IC50) values of 1.3 nmol/L and 0.035 nmol/L, respectively.[28] Cabozantinib strongly inhibited several kinases that have also been implicated in tumor pathobiology, including KIT, RET, AXL, TIE2, and FLT3 (IC50 = 4.6, 5.2, 7, 14.3, and 11.3 nmol/L, respectively). Cabozantinib did not potently inhibit kinases such as RON, EGFR, IGFR1, and EphA4/B4. In cellular assays, it inhibited phosphorylation of MET and VEGFR2, as well as KIT, FLT3, and AXL with IC50s of 7.8, 1.9, 5.0, 7.5, and 42 μmol/L, respectively.[28]

2.2.1 Nonclinical Development of XL184

In ***Vivo Activity***
In RIP-Tag2 transgenic mice (model of pancreatic neuroendocrine carcinoma), 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.[29] 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 (You *et al.*, 2011). Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein in tumors was slightly less, 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.[28] 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 impacted 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 pre-dose 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.[28]

Pharmacodynamics

In vivo pharmacodynamic experiments showed that XL184 inhibits key RTKs that promote tumor cell proliferation and/or angiogenesis (MET, VEGFR2, TIE-2, and RET) (Investigator's Brochure, 2010). In mice, the effective dose resulting in 50% inhibition (ED50) of targets was achieved at well tolerated doses of XL184 and at plasma exposures comparable to exposure observed in clinical trials. XL184 produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of 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 MET, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of XL184 resulted in significant inhibition of MET phosphorylation in TT tumors, with maximal inhibition of 70% seen at 60 mg/kg, relative to tumors from vehicle control-treated mice (Investigator's Brochure, 2011). Dose-dependent inhibition of phosphorylation of MET and RET was observed among the 3, 10, and 30 mg/kg dose groups.

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 MET [28]. This effect was reversible, as MET phosphorylation returned to basal levels by 48 hours after treatment.

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 (Investigator's Brochure, 2011). 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. 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.

2.2.2 Clinical studies with Cabozantinib

As of 4 May 2011, 1003 subjects have been enrolled in open-label clinical studies of cabozantinib, and 330 subjects have been enrolled in a placebo-controlled blinded Phase 3 study. Clinical data are available from nine studies of cabozantinib including four Phase 1 studies, one Phase 1b/2 study, three Phase 2 studies, and one Phase 3 study. Doses in the studies listed in Table 1 are in terms of salt-based dosing with the exception of study XL184-203, where the free-base equivalent weight is also noted.

Table 1.

Study #	Phase	Patient Population	Dose and Response
XL184-001	1	Solid tumors	Single-agent: Capsules: 25 and/or 100 mg PO daily (QD). 10 (29%) of 35 patients with MTC had a cPR[31]. Overall, of 85 patients with advanced solid tumors, 18 patients experienced tumor shrinkage of 30% or more, including 17 (49%) of 35 patients with MTC. In addition, 15 (41%) of 37 patients with MTC had SD for at least 6 months. In the non-MTC subset, SD of at least 3 months was reported in 38% of patients with the following tumors: colorectal (three patients); melanoma (two patients); carcinoid (two patients) tumors; and adenoid cystic, follicular thyroid, papillary thyroid, HCC, RCC, CTCL, salivary gland, ASPS, clear-cell sarcoma, mesothelioma, and neuroendocrine tumor originating in the thyroid (one patient each).
XL184-002	1	Newly diagnosed glioblastoma	XL184 qd in combination with TMZ and radiation therapy in the concurrent phase and with TMZ in the maintenance phase Arm 1, XL184: initiated at the start of 6–7 week concurrent phase of RT, given as a single agent during the 4-week rest phase, and continued subsequently in the maintenance phase. TMZ: starting dose of 75 mg/m^2/day QD with concurrent RT for 6 weeks. Arm 2, XL184: initiated during the maintenance phase with TMZ. TMZ: starting dose of 200 mg/m^2/day given 5 consecutive days and repeated every 28 days. MTD Expansion, XL184: initiated at the start of 6–7 week concurrent phase of RT, given as a single agent during

Study #	Phase	Patient Population	Dose and Response
			the 4-week rest phase, and continued subsequently in the maintenance phase. XL184 and TMZ will be given at MTDs determined in Arms 1 and 2.
XL184-008	1	Differentiated thyroid cancer (DTC) or metastatic RCC	Drug-drug interaction study with exploratory objective of anti-tumor activity. XL184: 175 mg PO QD. Rosiglitazone: one 4 mg dose followed by a second 4 mg dose 3 weeks later.
CA205-001	1	Advanced or metastatic solid tumors (Japan)	Starting dose: 75 mg PO QD; reduced to 50 mg. Study closed when collaboration with BMS was terminated
XL184-014	1	Advanced or metastatic solid tumors (Japan)	Starting dose 50 mg
XL184-202	1	NSCLC	Multiple dose levels of erlotinib + XL184 were evaluated. **Response**: The dose levels in phase 2 study XL184-202 are: arm B (75 mg XL184 + 150 mg erlotinib and 50 mg XL184 + 150 mg erlotinib [MTD]) and arm A (75 mg XL184 + 100 mg erlotinib; 125 mg XL184 + 100 mg erlotinib; and 125 mg XL184 + 50 mg erlotinib) (Wakelee *et al.*, 2010). Six of 36 evaluable patients, including at least 3 patients with prior erlotinib therapy, had 30% reduction in tumor measurements on at least 1 post-baseline scan, including 3 with a cPR (1 with MET amplification). Prolonged SD of 4 months was observed in some patients, including one patient for 9+ months and one patient with epidermal growth factor receptor (EGFR) T790M. A cPR was achieved in 5 of 64 (8%) evaluable patients enrolled in phase 1 (Investigator's Brochure, 2011). In phase 2, a cPR was observed in one patient treated with single-agent XL184.
XL184-201	2	Progressive or recurrent GB	Group A: initial dose of 175 mg. Groups B and C: initial dose of 125 mg. **Response**: at the dose of 125 mg QD, cPRs were observed in 11 of 37 (30%) patients without prior anti-angiogenic therapy, with a median duration of response of 5.1 months (range = 0.9–6.7) (Investigator's Brochure, 2011). At 175 mg QD, cPRs were observed in 7 of 34 (21%) patients without prior anti-angiogenic therapy, with a median duration of response of 2.9 months (range = 1.9–12.8).
XL184-203	2	Nine tumor-specific cohorts: breast cancer, gastric/GEJ adenocarcinoma,	Starting dose: 125 mg QD (100 mg freebase equivalent weight) during 12-weeks run-in phase. Patient with CR or PR continued XL184. Patients with SD were randomized to placebo or XL184 Patients with PD discontinued treatment.

Study #	Phase	Patient Population	Dose and Response
		HCC, melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, SCLC	Non-randomized extension cohorts in CRPC and ovarian cancer **Response:** One hundred seventy one CRPC subjects were enrolled. Randomization was suspended after 122 subjects were enrolled due to demonstrated clinical benefit. Seven patients achieved a cPR at week 12, and three additional patients achieved PR after the 12-week lead-in stage. The disease-control rate (rate of response +stable disease) at week 12 was 68%. Seventeen subjects were randomized to placebo; 14 to XL184. Among these subjects, the hazard ratio for PFS was 0.013 (p = 0.007). Of 108 subjects evaluable for bone scan response, 19% had complete resolution; 56% had partial resolution; 21% had stable disease and only 3% had progression as their best response. Three hundred nineteen subjects with non-CRPC advanced solid tumors were also enrolled in study XL184-203 .The overall ORR at week 12 by cohort was: HCC 10% (3/30 patients), NSCLC 10% (6/60 patients), breast 10% (2/20 patients), melanoma 5% (4/77 patients), SCLC 5% (1/21 patients), pancreatic 0% (0/20) and gastric/GEJ 0% (0/21). In 51 evaluable epithelial ovarian cancer patients, at 12 weeks, the overall RR was 24% (12/51 patients), 21% in platinum-refractory/resistant patients (7/34)), and 28% in platinum-sensitive patients (10/36). The highest disease control rates at week 12 were HCC (73%), ovarian (53%), melanoma (47%), breast (45%), and NSCLC (40%).
XL184-205	2	Grade IV astrocytic tumors	25 mg QD continuously (Arm 1); 75 mg QD continuously (Arm 2); 125 mg QD for two weeks followed by 50 mg QD continuously (Arm 3); and 125 mg QD on an intermittent 3 weeks on/1 week off schedule (Arm 4).
XL184-301	3	Unresectable, locally advanced or metastatic MTC	175 mg QD or placebo administered QD. **Response:** Randomized, double blind, placebo-controlled study recently reported top line data indicating that the primary endpoint of the study, PFS, was met. PFS on the cabozantinib arm was 11.2 months compared to 4 months on placebo, hazard ratio [HR] 0.28, p < 0.0001.

The dose of 60 mg proposed in this study is based on a recent trial reported at ASCO 2012 [30]. An adaptive response scheme was used to determine the lowest active daily cabozantinib dose among dose levels +1 (60 mg), 0 (40 mg), and -1 (20 mg). The primary endpoint was wk 6 bone scan response (BSR) assessed with an automated FDA 510(k) approved computer-aided detection system. A ≥30% decrease in total bone scan lesion area (BSLA) was defined as a response. The first cohort was treated at dose level 0. The number of responses (≥8 vs. <8 among 11 evaluable pts) was used to select the dose level (-1 vs. +1) for the second cohort. Based on the observed BSR rate in the second cohort of 11 patients, a dose was selected for expansion to treat 13 more pts. The study completed planned enrollment of 36 pts. Median age was 66; 44% were docetaxel-

pretreated. Among 12 pts enrolled at dose level 0, there were 10 BSRs at wk 6 including 1 complete response (CR), and 1 pt with stable disease (SD). The median decrease in BSLA was 62%. Ten patients evaluated at wk 12 included 9 BSRs (3 CRs), and 1 sustained SD. Among 11 pts then treated at dose level -1, 10 pts were evaluable at wk 6: 1 BSR, 5 SD, and 4 had progressive disease. No pts in the 2 cohorts required dose reduction or treatment interruption at 12 wks; 1 patient discontinued due to grade 3 AEs (anorexia, fatigue). 6/12 pts with ≥ 6 months follow-up remain on study. 5/5 pts enrolled at 40 mg with CTCs ≥5 per 7.5 mL converted to <5. Thirteen pts accrued to the expansion cohort at 40 mg daily had confirmed high BSR rate. The study concluded that cabozantinib 40 mg daily achieves a high BSR rate in men with CRPC and bone metastases, and is associated with better tolerability than previously reported for cabozantinib 100 mg daily. Hence, the manufacturer is carrying a dose of 60 mg forward in phase III trials, which is the dose that we have chosen in our trial.

Pharmacokinetics

In study XL184-001[31], pharmacokinetic (PK) analysis showed dose-proportional increases in plasma exposure (Cmax and AUC) both for the PIB formulation (dose range: 0.08 to 11.52 mg/kg) and the capsule formulation (dose range: 125 mg to 175 mg). After repeat daily dosing, t1/2, z values (mean ± standard deviation) for cabozantinib were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by day 15. 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 μg·h/mL; n = 23 *vs.* 41.6 ± 15.5 μg·h/mL; n = 23), indicating that cabozantinib accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Safety

As of March 1, 2011, the most frequently (>20%) observed adverse events (AEs) in 806 patients treated in single agent, open label cabozantinib studies, regardless of the relationship to drug, were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia and hypertension, (Investigator's Brochure, 2011). Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound healing complications, and proteinuria, have also been observed. As of 4 May 2011, of the 1003 subjects enrolled in open-label clinical trials with cabozantinib (either as a single-agent or in combination with other therapies). Across all open-label studies, the most common SAEs, regardless of causality were PE, dehydration, vomiting, DVT, pneumonia, diarrhea, nausea, convulsion, mental status changes, and abdominal pain. Fatigue (16%), diarrhea (10%), and nausea (6%) were the most common reasons for discontinuation. There have been 15 deaths considered related to cabozantinib treatment within 30 days of the last dose of study treatment: pulmonary embolism (2 patients), respiratory failure (pulmonary embolism) (1 patient), respiratory failure (1 patient), GI hemorrhage (2 patients), unexplained death (2 patients), hemoptysis (1 patient), hemorrhage intracranial (1 patient), enterocutaneous fistula (1 patient), respiratory disorder (1 patient), intestinal perforation (1 patient), hemorrhage (1 patient), and diverticular perforation–peritonitis (1 patient).

2.3 Correlative Studies

Substantial inhibition of phosphorylation of MET, RET, and KIT, as well as of downstream signaling molecules AKT and extracellular signal-regulated kinase (ERK), was seen following administration of cabozantinib (Investigator's Brochure, 2011).

From the first 12 cases in **study XL184-201**, 80% of samples of tumor cells were positive for MET with a lower fraction positive for RET and VEGFR2 (42% and 58%, respectively) (DePrimo *et al.*, 2009). MET signal in blood vessels was limited (33%); whereas, RET and VEGFR2 expression was often seen in tumor-associated blood vessels. Modulation of plasma levels of VEGFA, soluble MET, soluble VEGFR2, soluble KIT, and PlGF, was consistent with multiple on-target effects. Objective response was observed in the presence or absence of tumor EGFR amplification, phosphatase and tensin (PTEN) mutation, and O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation.

Phase 1: Study XL184-001 Changes in pharmacodynamic markers consistent with anti-angiogenesis activity were observed in Cohorts 6 through 12 and the eMTD Cohort with plasma samples taken on Day 1 pre-dose and Day 29. While small cohort sizes presented a challenge for statistical analysis of pharmacodynamic marker changes the combined data of Cohorts 12 and the eMTD Cohort (i.e., subjects enrolled at the MTD) demonstrated that changes in PlGF (↑), VEGF-A (↑), EPO (↑), and sVEGFR2 (↓) reached statistical significance. Soluble MET as a potential biomarker of MET inhibition was increased upon cabozantinib treatment and changes reached statistical significance.

One set of serial skin biopsies was received from a subject enrolled in the eMTD Cohort and was analyzed using fluorescence-based IHC. Changes in total MET, RET and KIT were minimal during the course of cabozantinib treatment but the activity (as assessed by the phosphorylation status) of these cabozantinib targets (decrease compared to baseline: MET: 40%, RET: 40%, KIT: 61%) as well as of the downstream signaling molecules AKT (39%) and ERK (55%) was statistically significantly reduced in this surrogate tissue. These observations support the on-target inhibitory effect of cabozantinib. Total levels and phosphorylation of VEGFR2 were not affected by cabozantinib treatment in this surrogate tissue.

2.3.1 Circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) in patients treated with MET and VEGFR inhibitors

Many proteins are proteolytically released from the cell surface by a process known as ectodomain shedding. Shedding occurs under normal physiologic conditions and can be increased in certain pathologies. MET is among the many receptors for which ectodomain shedding has been demonstrated. HGF stimulates mitogenesis, motogenesis, and morphogenesis in a variety of cellular targets during development, homeostasis, and tissue regeneration. Inappropriate HGF signaling resulting in unregulated cell proliferation, motility, and invasion occurs in several human malignancies. This can occur through paracrine signaling, autocrine loop formation, receptor mutation, gene amplification or gene rearrangement accompanied frequently with overexpression of ligand and/or receptor proteins. Working under the hypothesis that aberrant MET pathway activation in cancer might result in increased ectodomain shedding, MET could be a useful biomarker of tumor progression; Athauda et al. developed a sensitive

electrochemiluminescent immunoassay to quantitate MET protein in biological samples.[32] Their study showed significant direct correlations between malignant potential and sMET production in tumor-derived and genetically engineered cell lines, and between tumor burden and plasma sMET levels in mice harboring human tumor xenografts.[32] These preclinical studies supported the hypothesis that sMET might indicate malignant potential and/or tumor burden for cancers where the pathway is active.

Several studies of human clinical samples are now underway to investigate the potential utility of sMET to aid diagnosis and patient selection, and as a pharmacodynamic marker for drugs that directly target MET kinase activity. Among these is an ongoing collaboration between GlaxoSmithKline (GSK) and the NCI Urologic Oncology Branch to measure plasma sMET, HGF, VEGF-A and sVEGFR2 in patients in Phase I and II clinical trials of GSK1363089 (GSK089), an inhibitor of MET and VEGFR2 tyrosine kinases. In a Phase II gastric cancer study, patients treated with GSK089 on an intermittent dosing schedule showed significantly increased plasma sMET and VEGF-A during the treatment periods and decreases during drug holidays. Follow-up cell-based studies show that inhibition of MET kinase activity blocks receptor internalization, resulting in increased exposure to cell surface MET shedders(s), suggesting a direct short-term relationship between sMET levels and drug target inhibition. Increased VEGF-A levels have been reported as a response to VEGFR inhibitors in previous clinical studies. Median tumor burden did not change significantly over the course of the gastric study, so it was not possible to determine whether sMET levels could also reflect tumor burden. This question will be better assessed in an ongoing Phase II clinical trial of GSK089 in patients with papillary renal cell carcinoma, where changes in tumor burden meeting RECIST criteria were reported in an interim trial report.[33]

2.3.2 Circulating Tumor Cells (CTCs)

CTCs will be isolated from whole blood samples collected at baseline and then throughout the study for assessment of DNA damage response markers such as γH2AX. We will also evaluate whether we can measure changes in the number and phenotype (epithelial-mesenchymal transition) of CTCs in patients over time to explore any correlation with response to treatment or disease progression. This analysis will be performed in Dr. Kinders' lab with the ApoStream instrument, which uses antibody-independent CTC isolation technology that can isolate viable CTCs from epithelial and non-epithelial cancers.

2.4 Rationale

We propose a clinical trial of cabozantinib, a dual VEGFR and MET inhibitor, in refractory soft tissue sarcoma for the following reasons:

1. It has been shown that VEGF levels are elevated in patients with STS and correlates with the grade of the tumor.[14-17] Anti-VEGF agents like bevacizumab have been studied in this disease with promising results.[19,20] Pazopanib has also been studied in STS in phase II[21] and III settings[22]; patients showed improvement in PFS by 13 weeks compared to placebo.

2. Various sarcoma cell lines express high levels of activated c-Met receptor suggesting that HGF/SF signaling pathway may contribute to sarcomagenesis.[25] Interruption of autocrine or paracrine HGF/SF c-met signaling with the monoclonal antibody AMG102 in leiomyosarcoma cell line SK-LMS-1 and in mouse xenograft models has shown significant antitumor effect.[26] It has also been shown that MiT tumors like clear cell sarcoma cells are dependent on HGF/C-Met axis[27] for invasion, chemotaxis, and survival.

3. The MET pathway may play an important role in resistance to VEGF inhibitors like sunitinib.[34] Treatment with multiple VEGF inhibitors has been reported to be associated with an aggressive phenotype with increased invasiveness and higher MET expression.[35-37] Hence, we propose to target the dual arms of the VEGF/MET axis with cabozantinib in the hope to eliminate some of the resistance that has been encountered in the past with angiogenic inhibitors.

4. In vivo activity of XL184 has been shown in the form of tumor shrinkage in RIP-Tag2 transgenic mice[29] and mice bearing MDA-MB-231 cells[28]. As shown in Figure 3, combination blockade of VEGFR and c-MET with XL184 significantly ($P < 0.05$) prolongs survival compared to treatment with vehicle or anti-VEGFR antibody alone in the RIP-Tag2 transgenic mouse model, a spontaneous and highly vascularized pancreatic islet cell cancer.

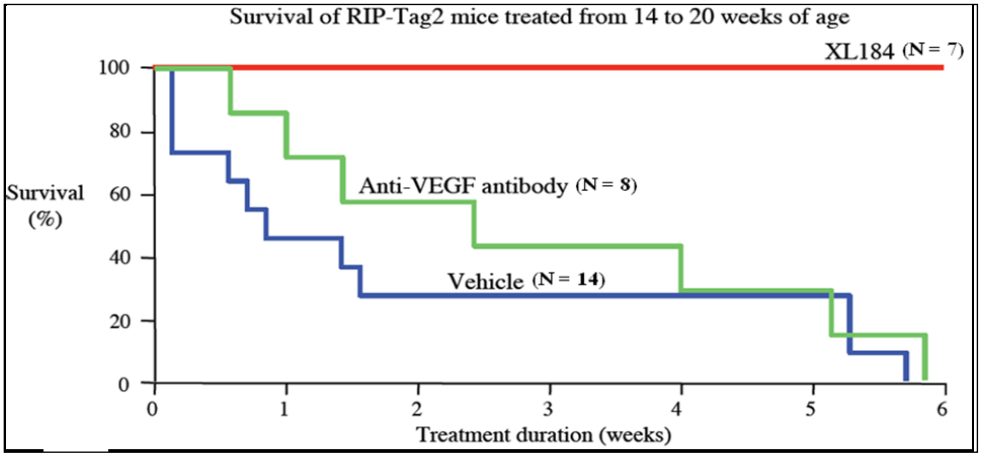

Figure 3: Increased survival of RIP-Tag2 transgenic mice following treatment with the VEGFR and c-MET inhibitor XL184 compared to treatment with anti-VEGF antibody or vehicle. The extent of liver metastasis was also less in RIP-Tag2 mice treated with combination blockade of VEGFR and c-MET than in mice treated with anti-VEGF antibody alone.

5. In the clinical arena, cabozantinib has been shown in Phase 1 study XL184-001 that evaluated the capsule formulation and suspension formulation to achieve SD of at least 3 months in advanced solid tumors (including one patient each of alveolar soft part sarcoma and clear cell sarcoma).[31]

By targeting the dual VEGF/c-MET pathway with cabozantinib in soft tissue sarcoma we propose to improve on the PFS that was established in the Phase III trial of pazopanib where it improved median PFS by 13 weeks compared to placebo.[22] If our proposed trial is positive, we

would anticipate this could lead to a large randomized phase III trial comparing the two targeted agents pazopanib and cabozantinib in STS, thereby establishing a new standard of care in this population.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed soft tissue sarcoma that is metastatic or unresectable and for which standard treatment that prolongs survival does not exist or is no longer effective.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral CT scan, MRI, or calipers by clinical exam.

3.1.3 Patients are allowed prior VEGFR-TKI therapy. Patients will be stratified based on prior VEGFR-TKI therapy.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of cabozantinib in patients <18 years of age, children are excluded from this study.

3.1.5 ECOG performance status ≤1 (Karnofsky >70%, see Appendix A).

3.1.6 Life expectancy > 3 months.

3.1.7 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 times ULN
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– creatinine	within normal institutional limits
OR	
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

– hemoglobin ≥9 g/dL
– serum albumin ≥2.8g/dL
– lipase <2.0 × ULN and no radiologic or clinical evidence of pancreatitis
– urine protein/creatinine ratio (UPCR) ≤1
– serum phosphorus calcium, magnesium and potassium ≥ LLN

3.1.8 Subjects must have blood pressure (BP) no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry provided that the average of three BP readings at the time of enrollment is ≤ 140/90 mmHg

3.1.9 Patients must be able to swallow whole tablets. Tablets must not be crushed or chewed.

3.1.10 The effects of cabozantinib on the developing human fetus are unknown. For this reason and because receptor tyrosine kinases are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception. 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).

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.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had anticancer therapy, including kinase inhibitors or any investigational agent within 4 weeks or 5 half-lives (whichever is shorter) (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered to baseline from adverse events (except alopecia and other non-clinically significant AEs). Patients who have received prior cabozantinib or inhibitors of c-MET or HGF are ineligible.

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

3.2.3 The subject has received radiation therapy within 4 weeks (≤ 2 weeks for palliative radiation therapy)

3.2.4 Patients with active brain metastases or carcinomatous meningitis or epidural disease are excluded from this clinical trial. Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation who are asymptomatic and have remained stable for 4 weeks 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 imaging with contrast-enhanced CT or

MRI scans for subjects with known brain metastases is required to confirm eligibility.

3.2.5 Eligibility of subjects receiving any medications or substances known to affect or with the potential to affect the activity of cabozantinib will be determined following review of their cases by the Principal Investigator (see Sections 3.2.8, 3.2.9 and 3.2.10 for further information). Patients who are taking enzyme-inducing anticonvulsant agents are not eligible.

3.2.6 Patients with refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that could interfere with absorption.

3.2.7 Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because cabozantinib has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib, breastfeeding should be discontinued if the mother is treated with cabozantinib.

3.2.9 Strong inhibitors and inducers of CYP3A4 can affect levels of cabozantinib and should be avoided whenever possible or switched to alternatives. Subjects requiring chronic concomitant treatment of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) are not eligible for this study. 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.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cabozantinib. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.11 The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g., clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted. (Please note that there may be cases in

which patients on study require anticoagulation for DVT/PE management; this does not necessitate taking the patient off study. See Section 6.1.5.)

3.2.12 The subject has experienced any of the following

- clinically-significant gastrointestinal bleeding within 3 months before the first dose of study treatment; the participant must be maintained on a prophylactic regimen for management of an upper GI bleeding event with no evidence of recurrence and/or endoscopic confirmation of resolution of the source of a lower GI bleed.
- hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment
- any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment

3.2.13 The subject has radiographic evidence of cavitating pulmonary lesion(s).

3.2.14 The subject has tumor invading or encasing any major blood vessels

3.2.15 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

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

1. Cardiovascular disorders including:

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

   b) Concurrent uncontrolled hypertension defined as sustained BP > 140 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment

   c) Any history of congenital long QT syndrome

   d) 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
      - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)

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

a) Any of the following within 28 days before the first dose of study treatment
- intra-abdominal tumor/metastases invading GI mucosa
- active peptic ulcer disease,
- inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
- malabsorption syndrome

b) Any of the following within 6 months before the first dose of study treatment:
- abdominal fistula
- gastrointestinal perforation
- bowel obstruction or gastric outlet obstruction
- 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 before the first dose of study treatment.

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

4. Other clinically significant disorders such as:

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

b) history of organ transplant, including allogeneic bone marrow transplant

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

d) history of major surgery as follows:

i. 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

ii. 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

3.2.17 The subject is unable to swallow tablets

3.2.18 The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before enrollment. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be

performed. If the average of these three consecutive results for QTcF is ≤500 ms, the subject meets eligibility in this regard.

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

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

3.2.21 Patients should not have any clinical evidence of an active infection at the time of enrollment.

3.3 Inclusion of Women and Minorities

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

3.4 Eligibility Screening Evaluation

3.4.1 Histologic confirmation: A block or stained slides of primary tumor tissue or of known recurrence will be required from each participant to confirm diagnosis. Pathology confirmation will be performed by the Laboratory of Pathology, NIH for patients enrolled at the NCI or by the department of pathology at the site where the patient is enrolled.

3.4.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and ECOG performance score) will be conducted within 8 days prior to enrollment.

3.4.3 Imaging Studies: All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI or CT scan with contrast of the brain, MRI liver, MRI for other disease sites, or bone scan may be done as clinically indicated.

3.4.4 Laboratory Evaluation: Laboratory data are to be obtained within 8 days prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, sodium, chloride, bicarbonate, calcium, creatinine, glucose, phosphorus, magnesium, potassium, total protein, SGOT [AST], SGPT [ALT], amylase, lipase, TSH.
- Serum or urine pregnancy test for female participants of childbearing potential.
- Urinalysis for urine protein/creatinine ratio or 24-hour urine for proteinuria if patients have 1+ or greater urine protein.
- EKG

4 REGISTRATION PROCEDURES

Eligible participants will be entered on study by a member of the study team.

4.1 Registration Process

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

Cohorts:
Cohort 1, Soft Tissue Sarcoma

Arms:
Arm 1, Cabozantinib

Arm Assignment:
Subjects in cohort 1 will be assigned to arm 1.

4.2 Participating Site Registration

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

To register a participant after they have signed the consent, complete Appendix F (Eligibility/Pre-Registration Worksheet) and fax (or email) it, along with all supporting records, to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, Fax (301) 451-5625, ashley.bruns@nih.gov. The Coordinating Center will notify you either by e-mail or fax that the protocol registration form has been received. The Coordinating Center will register the patient and provide the participating site with the patient's unique patient ID number. This unique ID number is to be used on all research samples and data entry for this patient. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, Fax (301) 451-5625, ashley.bruns@nih.gov.

4.3 Off Protocol Therapy and Off-Study Procedure

Status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

Participating sites: When a patient is taken off protocol therapy and when a patient is taken off-study, the Participant Status Updates Form included in Appendix F must be completed

and faxed or emailed to the Coordinating Center's Research Nurse, Ashley Bruns, Phone: (240) 858-3162, Fax (301) 451-5625, ashley.bruns@nih.gov.

5 TREATMENT PLAN

This is a multicenter phase II trial of patients with soft tissue sarcoma. Treatment will be administered on an outpatient basis.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, urinalysis, pregnancy test, and EKG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, pregnancy test, and EKG must be repeated prior to starting protocol therapy. Tumor imaging must be performed within 28 days prior to start of protocol therapy.

History and physical examination, labs (CBC with differential; serum chemistries), serum or urine pregnancy test (for female participants of childbearing potential), and EKG will be performed at baseline and within 8 days prior to the start of each new cycle after cycle 1. B12 and folate are not part of the screening evaluation but will be measured at baseline (within 8 days prior to start of protocol therapy) and every 12 weeks (every 3 cycles; within 8 days prior to the start of the cycle). Urinalysis for evaluation of urine protein/creatinine ratio should occur at baseline, within 8 days prior to the start of each new cycle after cycle 1, and as clinically indicated.

CT scans will be performed at baseline (within 28 days prior to start of protocol therapy), and repeat imaging scans will be performed every 2 cycles (every 3 cycles for patients on study for more than 1 year; every 4 cycles for patients on study more than 3 years). MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if in the opinion of the investigator this modality would provide a more accurate assessment of disease than a CT would for a given site.

The history and physical exam, pregnancy test, CT scan, EKG, and all other protocol-required labs, including blood collections for CTCs, will be done less frequently for patients on study more than one year (every 3 cycles after 1 year on study and every 4 cycles after 3 years on study). B12 and folate (measured at baseline and then every 3 cycles) will be measured every 4 cycles after 3 years on study.

5.1 Agent Administration

Adult patients will receive cabozantinib tablets as 60 mg tablets orally once a day in a 28-day cycle. A dose of 100 mg daily was tested and found to have acceptable efficacy albeit greater toxicity and a dose of 40 mg was also tested and found to be efficacious[30,38]. Patients who tolerate the 60 mg dose with little or minimal toxicity may be dose escalated to 80 mg after the first restaging (after cycle 2) for subsequent cycles. Dose escalation will be decided by the treating physician after discussion with the study PI. Adverse events and potential risks are described in Section 7. 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. Cabozantinib will be taken on an empty stomach, 1 hour before or 2 hours after food. Subjects may fast for at least 1 hour before and 2 hours after eating. The drug will be administered once daily at approximately the same time each day. Tablets must be swallowed whole and not crushed. A new cycle may begin up to 1 week later than it would otherwise be scheduled based on the 28-day cycle, to allow for flexibility for days the clinic is closed and other unexpected events.

Patients will be provided with a Study Diary (Appendix C), instructed in its use, and asked to bring it with them to each appointment. After cycle 2, a cycle will be considered completed if 90% of the prescribed doses are administered.

5.1.1 Cabozantinib

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. Concomitant medications that are inhibitors or inducers of the CYP3A4 pathway should be used with caution. Strong CYP3A4 inducers such as rifampin, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, St. John's Wort, and troglitazone should be avoided. In addition, 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 (Investigators brochure, 2011). Caution must also 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

Because there is a potential for interaction of cabozantinib 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. Appendix B presents guidelines for identifying medications/substances that could potentially interact 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/*).

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.

Cabozantinib is highly protein bound, 99.9%. Use caution when co-administering cabozantinib with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Administration of warfarin with cabozantinib is contraindicated as warfarin is highly protein-bound and has a very narrow therapeutic index.

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.

Avoid concomitant use of cabozantinib with proton pump inhibitors (PPIs) and H_2 -antagonists if possible. The PPIs and H_2 –antagonists may decrease cabozantinib plasma exposure levels and its effectiveness in humans. 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 cabozantinib. If needed, antacids are recommended for the initial treatment of dyspepsia or indigestion. If antacids are not adequate, the use of H_2 blockers (other than cimetidine) is preferred over PPIs. 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.

Potential Food Effect
The effect of food on the bioavailability of cabozantinib was evaluated in healthy adult subjects in a Phase 1; open-label, randomized, single-dose, two-treatment, and two-way crossover study (Study XL184-004). Based on the preliminary PK data, a high fat meal did not appear to alter the terminal $t_{1/2}$, but significantly increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib Cmax and AUC values by 41% and 57%, respectively. Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 1 hour before, and 2 hours after each cabozantinib dose).

5.2 General Concomitant Medication and Supportive Care Guidelines

All patients will be provided with the best available supportive care. No chemotherapeutic drugs other than cabozantinib will be allowed. Because there is a potential for interaction of cabozantinib 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 Anorexia

Anorexia leading to grade 3 weight loss will be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate or dronabinol may be considered. For Grade 3 weight loss dose reductions will not be done unless pharmacologic interventions have been tried first and fail.

5.2.2 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours (4 mg every 4 hours while asleep), till resolution of episode of at least 12 hours (no more than 16 mg of loperamide during a 24-hour period). This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours to ≤ Grade 2 with the above regimen (maximum of 16 mg of loperamide in a 24-hour period). If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated. The dose modification guidance in Table 6-1 should be followed. In addition, general supportive measures will 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.

5.2.3 Nausea and vomiting

Anti-emetics will not be administered routinely prior to cabozantinib. 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 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.

5.2.4 Myelosuppression

The use of growth factors will be considered in accordance with ASCO guidelines.

5.2.5 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.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Significant toxicity occurs despite 2 dose reductions as described in Section 6 or no lower dose level exists
- Patient decides to withdraw from the study
- 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.

5.4 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, and whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via biweekly phone calls.

5.5 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow up period or toxicities are unresolved but stabilized, patient withdraws from study, and/or patient enrolls on another protocol. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated to Central Registration per Section 4.

6 DOSING DELAYS/DOSE MODIFICATIONS

Treatment may be delayed for a maximum of 2 weeks for toxicities. In case toxicities do not resolve as stated, the patient will not receive further therapy on this protocol and will be followed for resolution of toxicities. Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Dose modifications are intended for within-cycle and start-of-next-cycle changes. If administration of study drug is interrupted for any reason, it will not be made up, and counting of the cycle days continues. A maximum of 2 dose reductions will be allowed before patient is taken off treatment. Patients who require a dose reduction will not have the dose re-escalated.

All patients begin at dose level 0. **Patients who tolerate dose level 0 with no or minimal toxicity may be escalated to 80 mg daily, sequentially, after the first restaging (after cycle 2).** Dose escalation will be decided by the treating physician after discussion with the study PI.

Table 3: Dose modification

Dose Level	Cabozantinib Dose
-2	20 mg
-1	40 mg
0	60 mg
+1	80 mg

6.1 Management of Cabozantinib-related AE

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities**.

6.1.1 General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 6-1 and Table 6-2, respectively.

These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study chair is recommended**.**

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 5 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib 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 does resolves to resolves to Grade ≤1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or	• Interrupt cabozantinib 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, cabozantinib may be resumed at either the same dose or with a

which is easily managed by medical intervention or resolved quickly	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, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 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 and sponsor but only with sponsor approval.
Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.	

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

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 reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until platelet count is ≥100,000/mm^3, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤1 and temperature to ≤ 38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.

CTCAE Version 5 Grade	Intervention
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** (Platelet count <LLN – 75 x 10^9/L); **Grade 2** (Platelet count <75.0 – 50.0 x 10^9/L); **Grade 3** (Platelet count <50 - 25 × 10^9/L); **Grade 4** (Platelet count < 25 × 10^9/L).	

6.1.2 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 or until LFTs return to baseline or stabilize at grade 1. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with weekly monitoring of LFTs for 2 weeks or until LFTs return to ≤ Grade 1 or baseline. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with weekly LFTs for 4 weeks or 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.

Transaminase elevation CTCAE v5.0	Intervention
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 from baseline AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with weekly monitoring of LFTs for 4 weeks or until LFTs return to baseline or stabilize, whichever occurs first. If LFTs continue to rise but remain ≤5.0 x ULN continue to monitor LFTs weekly for 4 weeks. If LFTs continue to rise after the additional 4 weeks of monitoring, 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 from baseline 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.

6.1.3 Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended

that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

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.

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.

6.1.4 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.

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.

6.1.5 Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigators Brochure). 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 experimental treatment 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. *Note:* lovenox will be administered as therapeutic anticoagulation; no data exist of an interaction between cabozantinib and lovenox.

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.

6.1.6 Hypertension toxicity

Therapeutic BP monitoring by a health care provider will occur at the beginning of every cycle for the duration of treatment .All patients will be required to monitor their BP at least once a day (preferably BID) throughout the treatment and record the readings in the study diary (Appendix C). Subjects with known hypertension should be optimally managed prior to study entry. 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 4 below).

If the readings are abnormal the patient needs to have the BP reconfirmed by a health care provider prior to changes in study drug or antihypertensive medications are made. Table 4 will be used for the management, and for the determination of cabozantinib dose modification. Suggested antihypertensive medications are listed in Appendix D.

Table 4

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.
≥ 180 mm Hg (systolic)	• Interrupt treatment with cabozantinib Add new or additional anti-

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
OR ≥ 120 mm Hg (diastolic)	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	

6.1.7 Proteinuria toxicity

Evaluation of urine protein/creatinine ratio (UPC) should occur as follows: at baseline and at the start of each cycle. Dose modification should be done according to Table 5 below.

Severity of Proteinuria Urine Protein/Creatinine Ratio	Management of Proteinuria
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• Confirm with a 24 hour urine protein excretion within 7 days. • If proteinuria of > 1 g/24 hours is confirmed, hold cabozantinib and continue with UPCR monitoring. When UPCR returns to < 1, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephritic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephritic 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 decreased to < 1, then revert to UPCR monitoring frequency specified in protocol

UPCR, urine protein/urine creatinine ratio.

6.1.8 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 (2.5 mL) 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 abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

6.1.9 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.

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

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

GI-perforation/fistula:
- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis .
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess

- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

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

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with 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.

6.1.11 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.

6.1.12 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.

6.1.13 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.

6.1.14 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 EKGs 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 EKGs should be performed within 30 minutes after the initial EKG with intervals not less than 3 minutes apart. If the average QTcF from the three EKGs 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 EKG 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.

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) 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 CAEPR for Cabozantinib (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).

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		

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%)**	
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			
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	

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%)**	
		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 CTEP Reporting Requirements

7.2.1 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 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.2.4.

- **Attribution** of the AE:
  1. Definite – The AE *is clearly related* to the study treatment.
  2. Probable – The AE *is likely related* to the study treatment.
  3. Possible – The AE *may be related* to the study treatment.
  4. Unlikely – The AE *is doubtfully related* to the study treatment.
  5. Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2.2 Expedited Adverse Event Reporting

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/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.2.3).

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.

7.2.3 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients

7.2.4 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 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." 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.

Phase 1 and Early Phase 2 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 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[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

7.2.5 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Lymphopenia (any grade), alopecia (any grade), anemia (grade 2), electrolytes (grade 2: sodium, potassium, phosphorous, and magnesium), albumin (grade 2), hyperuricemia (grade 3), INR (grade 2), and PTT (grade 2) will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.2.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.2.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.2.8 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.

7.2.9 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.

7.2.10 Multicenter Guidelines for Expedited Adverse Event Reporting

7.2.10.1 **Expedited Adverse Event Reporting for Participating Sites**

Adverse Event Reporting via CTEP-AERS:
Follow sponsor expedited AE reporting requirements in Section 7.2 and copy Ashley Bruns (ashley.bruns@nih.gov) and Dr. Alice Chen (chenali@mail.nih.gov) on all CTEP-AERS reports.

Adverse Event Reporting to NIH IRB:
The Coordinating Center will review CTEP-AERS reports and submit to the NIH-IRB via iRIS (https://iris.nci.nih.gov/iMedris/). The site PI must immediately report to the Coordinating Center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The site PI must also report any protocol deviations or violations to the Coordinating Center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

Follow NIH IRB expedited AE reporting requirements in this section. Complete the NIH IRB Expedited AE form supplied by the Coordinating Center. Send the completed form to Ashley Bruns either by e-mail to ashley.bruns@nih.gov or by fax to (301) 451-5625.

7.3 NIH Reporting Requirements

7.3.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events (https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs).

7.3.2 OHSRP Office of Compliance and Training / IRB Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.3.3 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

7.3.4 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP/IRB in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the NCI Clinical Director or their designee atNCICCRQA@mail.nih.gov within one business day of learning of the death.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with cabozantinib can be found in Section 7.1.

8.1 Cabozantinib (NSC 761968)

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

Other Names: XL184, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: $C_{28}H_{24}FN_3O_5.C_4H_6O_5$
Molecular Weight: 635.6

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

How Supplied: Cabozantinib is supplied by Exelixis and distributed by the DCTD. Cabozantinib is available in 20-mg and 60-mg tablets. 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 30 tablets per bottle.

Cabozantinib Tablet Components and Composition

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

Storage: Store intact bottles at controlled room temperature, 20° to 25°C (68° F to 77° F); temperature excursions are permitted between 15° C and 30° C (59° F to 86° F) [see USP Controlled Room Temperature].

If a storage temperature excursion is identified, promptly return cabozantinib to 20° to 25°C (68° to 77° F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact bottles is ongoing. Cabozantinib is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

Route of Administration: Oral cabozantinib should be taken on an empty stomach, 1 hour before or 2 hours after food. Do not crush or chew.

Potential Drug Interactions: See Section 5.1.1

8.2 Agent Ordering

NCI-supplied agents may be requested by the responsible 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), Biosketch, Agent Shipment Form, 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://ctepcore.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.

8.3 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9 CORRELATIVE STUDIES

9.1 Pharmacodynamics

Blood will be obtained from all patients for PD assessment as described in Section 9.1.1. Optional blood samples will also be collected for isolation of CTCs as defined in Section 9.1.2.

Record the date, planned time, and actual time of collection for each specimen on the PK/PD Sample Collection Sheet in Appendix H, the CTEP tracking number (P9284), unique patient accession number, and 3-digit sample number should be included on this form. In addition, the date and exact time when study drug was administered should be recorded on the form.

At the NCI, at least 24 hours prior to blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail NCIPK-PDsupportgroup@mail.nih.gov Pager: 102-12798 Phone: 301-451-1169 Fax: 301-480-5871.

9.1.1 Blood Samples (mandatory at the NCI but optional at participating sites)

Assays to be performed: sMET, HGF, VEGF-A, and sVEGFR2. These research blood tests are mandatory at the NCI but optional at participating sites:

Samples will be obtained at the following time points:

- Before drug administration on study (baseline)
- Cycle 1 day 1; 3-6 hours post dose
- Cycle 2 day 1; 3-6 hours post-dose

1. Blood samples should be obtained using EDTA as an anticoagulant; the minimum volume of blood needed for analysis of all four markers is 3 mL
2. Plasma should be prepared from the blood samples within 1 hour (with interim storage and handling at 4ºC).
3. Plasma should be transferred to a sterile screw cap cryovial (silicon gasket); pre-labeled with bar code is preferred.
4. Plasma should be frozen and stored at -80°C within 1 hour of blood processing.
5. Samples should be shipped on dry ice in batches at periodic intervals (if local storage is limiting or interim analysis is performed) or after all samples have been collected.

Samples should be shipped to:

Donald P. Bottaro, PhD
Urologic Oncology Branch
National Cancer Institute
Bldg 10, Rm 1W-5832
10 Center Drive MSC 1210
Bethesda, MD 20892-1210
301-496-6353 (UOB Office & paging)
301-402-6499 (direct & voice mail)
301-402-0922 (fax)

bottarod@mail.nih.gov

Participating sites should e-mail the research nurse, Ashley Bruns, at ashley.bruns@nih.gov prior to sending samples to obtain a FedEx account number to use for shipment.

9.1.2 Blood Collection for Circulating Tumor Cells (optional)

Whole blood will be collected aseptically by venipuncture or from a venous port into one 6-mL sodium heparin tube.

Blood samples for CTCs (optional) will be collected at the following times:

- cycle 1 prior to drug administration (baseline)
- cycle 1 day 1 4 hours (+/- 1 hour) after drug administration
- day 1 of every subsequent cycle prior to drug administration (every 3 cycles after 1 year on study and every 4 cycles after 3 years on study)
- one additional blood sample will be collected at time of disease progression

Testing and data analysis will be performed by Dr. Bob Kinders (PADIS/FNLCR).

Samples should be shipped to:
Attention: Dan Danner
NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21701
Phone: 301-846-5748
NCI_PD_Support_CellSearch@mail.nih.gov

Blood for CTC analysis will be shipped to the PADIS laboratory on the day it is collected. Shipping arrangements will be made by sending an email to NCI_PD_Support_CellSearch@mail.nih.gov**.**
For NCI Clinical Center specimens only: arrangements will be made for pickup with the CSP courier service (301-846-5893)

9.1.3 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions.

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. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
300 series: blood for PD
400 series: blood for circulating tumor cells (CTCs)

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. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. 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.

Any new use of these samples will require prospective IRB review and approval. 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.

9.1.4 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
X De-identified data in an NIH-funded or approved public repository
X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
X An NIH-funded or approved public repository: clinicaltrials.gov
X BTRIS (automatic for activities in the Clinical Center)

X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

10 STUDY CALENDAR

Eligibility screening evaluations are to be conducted within 8 days prior to enrollment, with the exception of informed consent and tumor imaging scans, which must be done within 28 days prior to enrollment (see Section 3.4). Baseline history, physical examination, laboratory evaluations, urinalysis, pregnancy test, and EKG are to be conducted within 8 days prior to the start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, pregnancy test, and EKG must be repeated prior to starting protocol therapy. Baseline imaging scans and must be done within 28 days prior to the start of protocol therapy.

A new cycle may begin up to 1 week later than it would otherwise be scheduled based on the 28-day cycle, to allow for flexibility for days the clinic is closed and other unexpected events. 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.

	Pre-Study Screening	C1 W1	C1 W2	C1 W3	C1 W4	C2 W1	C2 W2	C2 W3	C2 W4	C3 W1	C3 W3	Off Treatment
Cabozantinib[a]		X	X	X	X	X	X	X	X	X	X	
Informed consent	X											
Archival tumor[b]	X											
Demographics	X											
Medical history	X											
Concurrent meds	X	X----------									----------X	
Physical exam[c,m]	X	X[n]				X				X		
Vital signs[d,m]	X	X[n]				X				X		
Height	X											
Weight[m]	X	X[n]				X				X		
Performance status[m]	X	X[n]				X				X		
CBC w/diff, plts[e,m]	X	X[n]				X				X		
Serum chemistry[e,m]	X	X[n]				X				X		
B12, folate[o]		X										
Urine protein/ creatinine ratio[f,m]	X	X[n]				X				X		
Adverse event evaluation		X----------									----------X	
Tumor measurements[g,m]	X	Tumor measurements as indicated below. Documentation (radiologic) must be provided for patients removed from study for progressive disease.										
EKG[h,m]	X	X[n]				X				X		
B-HCG[i,m]	X	X[n]				X				X		
PD blood sampling[j]		X				X						
TSH[k,m]	X	X[n]				X				X		
Blood for CTCs[l,m]		X				X				X		X

a: Cabozantinib once daily at 60 mg po daily. A new cycle may begin up to 1 week later than it would otherwise be scheduled based on the 28-day cycle, to allow for flexibility for days the clinic is closed and other unexpected events.

b: Archival tumor specimens will be requested to confirm diagnosis and is mandatory for eligibility in the trial.

c: Physical examination should be performed at baseline and within 8 days prior to the start of each new cycle.

d: BP monitoring by a health care provider should be performed within 8 days prior to the start of each new cycle. Patients should measure and record their blood pressure at home at least once per day for the duration of the study.

e: Serum chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, sodium, chloride, bicarbonate, calcium, creatinine, glucose, amylase, lipase, phosphorus, magnesium, potassium, total protein, SGOT [AST], SGPT [ALT]) and CBC w/diff, platelets at baseline and within 8 days prior to the start of each new cycle.

f: Evaluation of urine protein/creatinine ratio should occur at baseline, within 8 days prior to the start of each new cycle, and as clinically indicated. If patient has urine protein/creatinine ratio >1+, obtain a 24 hour urine for protein and creatinine clearance.
g: Tumor measurements are repeated every 2 cycles (every 3 cycles for patients on study for more than 1 year; every 4 cycles for patients on study more than 3 years).
h: EKG will be performed at baseline and within 8 days prior to the start of each new cycle.
i: Serum or urine pregnancy test (women of childbearing potential) at baseline and within 8 days prior to the start of each new cycle.
j: Blood samples will be obtained at the following time points: at baseline, on C1D1 3-6 hours after dose of cabozantinib and C2D1 3-6 hours post drug (mandatory at the NCI but optional at participating sites).
k: TSH at baseline and within 8 days prior to the start of each new cycle.
l: Blood for circulating tumor cells (CTCs) will be collected (optional) as described in Section 9.1.2.
m: The history and physical exam, pregnancy test, CT scan, EKG, TSH, and all other protocol-required labs and CTC blood collections will be done every 3 cycles after 1 year on study and every 4 cycles after 3 years on study.
n: Eligibility screening results may be used for these baseline measurements if conducted within 8 days prior to the start of protocol therapy. See Sections 3.4 and 5.
o: B12 and folate at baseline and every 12 weeks (every 3 cycles, within 8 days prior to the start of the cycle; every 4 cycles after 3 years on study).

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks or 2 cycles (every 3 cycles for patients on study for more than 1 year; every 4 cycles for patients on study more than 3 years). In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. Bone scans will be done at baseline for patients with known bone tumors and at restaging if clinically needed.

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]. 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 cabozantinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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 ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥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.

11.2 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.

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-PET: While 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.

11.3 Response Criteria

11.3.1 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.

11.3.2 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).

11.3.3 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		

11.4 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 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.

11.5 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 REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

Data will be collected in the Center for Cancer Research C3D database. This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. 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: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP. The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 Data Safety and Monitoring Plan

The investigators at each participating center will be responsible for the collection, maintenance, and quality control of the study data. Adverse events observed in patients enrolled on the trial will be monitored in real time by the Principal and Associate Investigators, and attribution of these events to the research will be determined at the end of each treatment cycle in each subject. The clinical research team (PI, adjunct PI, research nurses, data managers) will meet weekly when patients are being actively treated on the trial to discuss each patient in detail and ensure that all events are graded appropriately, and that the attribution to study drug is correct. The Coordinating Center is responsible for establishing conference calls between participating sites at least on a monthly basis to discuss the observed toxicities and protocol issues.

All SAEs will be reported through CTEP-AERS to CTEP, to the Coordinating Center PI at NCI, and forwarded to the IRB per Section 7.0. In all cases where the dose of the study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to the study treatment, the investigator must contact and inform the Coordinating Center PI. All sites will be monitored by the CTEP drug monitor, who will receive data from all participating sites.

Data will be monitored regularly by the PI in order to identify significant toxicity trends. Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients.

Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the FDA or other authorized user, only under guidelines established by the Federal Privacy Act.

Safety Monitoring Committee:
Because this is a multi-institutional protocol for which the NCI CCR is the Coordinating Center, it will be monitored by the DTC Safety Monitoring Committee, NCI.

12.3 Multicenter Guidelines

This protocol opened initially at the NCI. The NIH IRB will be notified once the participating centers' IRBs have approved the studies to open. This protocol will follow the CCR's Clinical Research Operations' SOPs for multicenter trials.

12.3.1 IRB Approvals

As the Coordinating Center for a trial, it is the PI's responsibility to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the NIH IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before NIH IRB approval will be granted.

The PI will provide the NIH IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH IRB.

12.3.2 Amendments and Consents

The NCI PI will provide the NIH IRB with copies of all amendments, consents, and approvals from each participating institution.

12.3.3 Data Collection

The investigators will be responsible for the collection, maintenance, and quality control of the study data. All data collected for each study subject will be entered into the Cancer Central Clinical Database (C3D), an NCI electronic case report form/database, every 2 weeks. The participating sites will be able to enter the data remotely into the web-based C3D system. Each site investigator is also responsible for maintaining all source documentation related to the study, including any films, tracings, computer discs or tapes. NCI will be responsible for data management, data analysis, and reporting. Data collection forms will be provided to the participating institutions. Required data include, not exclusively: prior disease-related therapies with dates, disease type, stage, disease sites, with measurements, and concurrent medications.

12.3.4 Data and Center Audits

Audits will be conducted yearly to ensure data integrity and provide quality control. These audits will be conducted by the NCI research team. Selected patient charts should be audited as well as the participating institution's Standard Operating Procedures (SOP) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

12.3.5 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix E.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) (except for Group studies).

12.4 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.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The study will be conducted as a dual-endpoint two-stage Phase II trial to target objective tumor response rate (CR+PR) of 30% against an unacceptably low rate of 10%, and 6-month PFS rate of 65% against an unacceptably low rate of 45% (corresponding to median PFS of 9.6 vs. 5.2 months).

The trial is designed to accrue up to 50 evaluable patients and judge the agent as promising if either tumor response rate or 6-month PFS rate is promising. If at least 11 objective responses (at least 22%), or at least 27 instances of 6-month PFS (at least 54%), are observed among the 50 evaluable patients, this agent will be considered worthy of further testing in this disease. If no more than 3 objective responses (12%), and no more than 12 instances of 6-month PFS (no more than 48%), are observed among the initial 25 patients, the study will be terminated early and declared negative. This design yields at least 90% power to detect a true objective response rate of at least 30%. It yields at least 92% power to detect a true 6-month PFS rate of at least 65% (median PFS of 9.6 months). It yields at least .89 probability of a negative result if the true objective response rate is no more than 10% and the true 6-month PFS rate is no more than 45% (median PFS of 5.2 months), with approximately .53 probability, at least, of early negative stopping in this case. These last two probabilities (of a negative result and early negative stopping, both under the null hypothesis) are calculated assuming that tumor response rate and PFS rate are uncorrelated. If they are positively correlated, as is likely, the probabilities will be a bit higher.

13.2 Sample Size/Accrual Rate

The study will accrue 50 evaluable patients at the rate of 2-3 patients per month. To allow for a small number of unevaluable patients, the accrual ceiling has been set at 55 patients.

13.3 Stratification Factors

Patients will be stratified based on prior VEGF/TKI therapy. In order to ensure accrual of multiple different histological types of STS to this trial (including histologic types that are felt to be driven by angiogenesis or the MET pathway), following accrual of the first 20 patients, discussions will be held with CTEP to review which other histologic types of STS should be enrolled.

13.4 Analysis of Secondary Endpoints

- Determine and compare circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of cabozantinib.
- All PD changes from baseline will be assessed descriptively by calculating the mean and the 95% confidence interval of the change. PD measures derived from blood samples will be used to assess the change from baseline 3-6 hours after the first dose of the first cycle of treatment and 3-6 hours after the first dose of the second cycle of treatment.

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 will 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) will be included in the main analysis of the response rate. Patients in response categories 4-9 will 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 will 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 will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Justification for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of cabozantinib on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that

cabozantinib may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to cabozantinib. HIV-positive patients on combination antiretroviral therapy are excluded from the study because of possible interactions with cabozantinib

14.1.1 Participation of Children

This study includes patients 18 years of age and older. Because insufficient dosing or adverse event data are currently 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. Studies will be performed in patients <18 years of age when it is appropriate to do so.

14.2 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Sections 5 and Section 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.3 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

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 (*i.e.*, long-term stabilization and/or improvement in the pain and physical impairment caused by soft tissue sarcoma), all subjects ≥ age 18 **at the NCI only** 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 for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH OHSRP Policy 403 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 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

14.5 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A:PERFORMANCE STATUS CRITERIA

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

APPENDIX B: POTENTIAL DRUG INTERACTIONS

Because the lists of these agents are constantly changing, frequently-updated lists available at http://medicine.iupui.edu/clinpharm/ddis/table.asp will be consulted.

CYP3A4 Inhibitors

Acetazolamide	Danazol	Grapefruit juice	Nefazodone	Risperidone
Amiodarone	Dasatinib	Haloperidol	Nelfinavir	Ritonavir
Amlodipine	Delavirdine	Hydralazine	Nevirapine	Saquinavir
Amprenavir	Desipramine	Ifosfamide	Nicardipine	Selegiline
Anastrozole	Dexmedetomidine	Imatinib	Nifedipine	Sertraline
Aprepitant	Diazepam	Indinavir	Nisoldipine	Sildenafil
Atazanavir	Diclofenac	Irbesartan	Nizatidine	Sirolimus
Atorvastatin	Dihydroergotamine	Isoniazid	Norfloxacin	Sulconazole
Azelastine	Diltiazem	Isradipine	Olanzapine	Tacrolimus
Azithromycin	Disulfiram	Itraconazole	Omeprazole	Tamoxifen
Betamethasone	Docetaxel	Ketoconazole	Orphenadrine	Telithromycin
Bortezomib	Doxorubicin	Lansoprazole	Oxybutynin	Teniposide
Bromocriptine	Doxycycline	Lidocaine	Paroxetine	Testosterone
Caffeine	Drospirenone	Lomustine	Pentamidine	Tetracycline
Cerivastatin	Efavirenz	Losartan	Pergolide	Ticlopidine
Chloramphenicol	Enoxacin	Lovastatin	Phencyclidine	Tranylcypromine
Chlorzoxazone	Entacapone	Mefloquine	Pilocarpine	Trazodone
Cimetidine	Ergotamine	Mestranol	Pimozide	Troleandomycin
Ciprofloxacin	Erythromycin	Methadone	Pravastatin	Valproic acid
Cisapride	Ethinyl estradiol	Methimazole	Prednisolone	Venlafaxine
Clarithromycin	Etoposide	Methoxsalen	Primaquine	Verapamil
Clemastine	Felodipine	Methylprednisolone	Progesterone	Vinblastine
Clofazimine	Fentanyl	Metronidazole	Propofol	Vincristine
Clotrimazole	Fluconazole	Miconazole	Propoxyphene	Vinorelbine
Clozapine	Fluoxetine	Midazolam	Quinidine	Voriconazole
Cocaine	Fluvastatin	Mifepristone	Quinine	Zafirlukast
Conivaptan	Fluvoxamine	Mirtazapine	Quinupristin	Ziprasidone
Cyclophosphamide	Fosamprenavir	Mitoxantrone	Rabeprazole	
Cyclosporine	Glyburide	Modafinil	Ranolazine	

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John's wort
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz	Levonorgestrel	Rifabutin
Aprepitant	Eletriptan	Lidocaine	Rifampin
Aripiprazole	Enalapril	Losartan	Ritonavir
Atazanavir	Eplerenone	Lovastatin	Saquinavir
Atorvastatin	Ergoloid mesylates	Medroxyprogesterone	Sertraline
Benzphetamine	Ergonovine	Mefloquine	Sibutramine
Bisoprolol	Ergotamine	Mestranol	Sildenafil
Bortezomib	Erythromycin	Methadone	Simvastatin
Bosentan	Escitalopram	Methylergonovine	Sirolimus
Bromazepam	Estradiol	Methysergide	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Miconazole	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Midazolam	Tamoxifen
Buspirone	Estrogens, conj., esterified	Miglustat	Tamsulosin
Busulfan	Estrone	Mirtazapine	Telithromycin
Carbamazapine	Estropipate	Modafinil	Teniposide
Cerivastatin	Ethinyl estradiol	Montelukast	Terbinafine
Chlordiazepoxide	Ethosuximide	Moricizine	Tetracycline
Chloroquine	Etoposide	Nateglinide	Theophylline
Chlorpheniramine	Felbamate	Nefazodone	Tiagabine
Cisapride	Felodipine	Nelfinavir	Ticlopidine
Citalopram	Fentanyl	Nevirapine	Tolterodine
Clarithromycin	Flurazepam	Nicardipine	Toremifene
Clobazam	Flutamide	Nifedipine	Trazodone
Clonazepam	Fosamprenavir	Nimodipine	Triazolam
Clorazepate	Fulvestrant	Nisoldipine	Trimethoprim
Cocaine	Gefitinib	Nitrendipine	Trimipramine
Colchicine	Halofantrine	Norethindrone	Troleandomycin
Cyclophosphamide	Haloperidol	Norgestrel	Vardenafil
Cyclosporine	Ifosfamide	Ondansetron	Venlafaxine
Dantrolene	Imatinib	Paclitaxel	Verapamil
Dapsone	Indinavir	Pergolide	Vinblastine
Delavirdine	Irinotecan	Phencyclidine	Vincristine
Diazepam	Isosorbide dinitrate	Pimozide	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pioglitazone	Zolpidem
Dihydroergotamine	Isradipine	Primaquine	Zonisamide
Diltiazem	Itraconazole	Progesterone	Zopiclone
Disopyramide	Ketamine		

APPENDIX C: STUDY DIARY

Today's date _____ **Agent: Cabozantinib**

Patient Name_____(*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. Cabozantinib should be taken with water at least 1 hour before or 2 hours after a meal. The drug tablets should be swallowed whole with water and may not be crushed or broken.
3. Do not chew the tablets. If the tablet is broken and the powder of the tablets gets on skin, wash the exposed area with as much water as necessary. Inform investigator or nurse if that occurs.
3. Record the date and times when you took the tablet/s.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottle of cabozantinib when you return for your Day 28 appointment.
6. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Cabozantinib tablet strength 20 mg	60mg	Time of Cabozantinib dose	Blood Pressure Morning	Evening	Comments Side effects / missed dose
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Patient's signature _____

APPENDIX D: DRUG INTERACTIONS

Oral Antihypertensive Medications: Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cabozantinib through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	25 mg daily	50 mg daily	100 mg daily	No
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	5 mg daily	10-20 mg daily	40 mg daily	No
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: perindopril	4 mg daily	none	8 mg daily	Yes, but not CYP450
	Rarely used: quinapril	10 mg daily	20 mg daily	40 mg daily	No
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	40 mg daily	none	80 mg daily	Yes, but not CYP450
	valsartan	80 mg daily	none	160 mg daily	Yes, but not CYP450
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

APPENDIX E: CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP Form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
- Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP (See Section 8). Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

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Appendix F: Eligibility/Pre-Registration Worksheet

Coordinating Center: NCI
Bethesda, MD 20892
Contact: Ashley Bruns
Tel: (240) 858-3162
Fax: (301) 451-5625
ashley.bruns@nih.gov

PI: A. P. Chen, MD
240-781-3320
chenali@mail.nih.gov

<table>
<tr><td colspan="2">Patient's Name: (FML)</td><td>Institution:</td></tr>
<tr><td colspan="2">Medical Record Number:</td><td>Investigator:</td></tr>
<tr><td colspan="2">Patient's Birth date:</td><td rowspan="2">Signature of Treating Physician</td></tr>
<tr><td colspan="2">Sex: _____male _____female</td></tr>
<tr><td colspan="2">IRB approval valid until (date):</td><td>Date Informed Consent was signed:</td></tr>
<tr><td>Race:
_____ Black
_____ Caucasian
_____ Asian
_____ American Indian
_____ Native Hawaiian/Pacific Islander
_____
Other_____</td><td>Ethnicity:
___Hispanic
___Non-Hispanic
___Other:</td><td>Projected start date of treatment:</td></tr>
</table>

Continued next page

INCLUSION CRITERIA: All responses must be YES. A NO response will make the subject ineligible.

	Yes	No	N/A
Does the patient have histologically or cytologically confirmed soft tissue sarcoma that is metastatic or unresectable and for which standard treatment that prolongs survival does not exist or is no longer effective?			
Does the patient have measurable or evaluable disease?			
Has the diagnosis of malignancy been confirmed by the department of pathology at the institution where the patient is being enrolled?			
Has the patient completed any previous anticancer therapy, including kinase inhibitors or any investigational agent, at least 4 weeks or 5 half-lives (whichever is shorter) (6 weeks for nitrosoureas or mitomycin C) prior to entering the study and recovered to baseline from adverse events (except alopecia and other non-clinically significant AEs)? Patients who have received prior cabozantinib or inhibitors of c-MET or HGF are ineligible.			
Does the subject have blood pressure (BP) no greater than 140 mmHg (systolic) and 90 mmHg (diastolic)?			
Age ≥ 18 years?			
Karnofsky score > 70% (see Appendix A) score_____ or ECOG ≤ 1?			
Life expectancy > 3 months?			
Has the patient, if a woman of childbearing potential or a man, agreed to use adequate birth control?			
Has a signed informed consent/assent been obtained?			
Able to swallow whole tablets?			

EXCLUSION CRITERIA: Responses should be NO

	Yes	No	N/A
Does the patient have any clinically significant illnesses which would compromise participation in the study, including, but not limited to known HIV infection requiring combination antiretroviral therapy, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, gastrointestinal disorders associated with a high risk of perforation or fistula formation, or psychiatric illness/social situations that would limit compliance with study requirements?			
Does the patient have known brain metastases, carcinomatous meningitis, or epidural disease? Patients whose brain metastatic disease status has remained stable for 4 weeks after treatment and do not require steroid treatment for at least 2 weeks before starting the study are eligible.			
Is the patient taking enzyme-inducing anticonvulsant agents?			
Does the patients have refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that could interfere with absorption?			
Does the subject require concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g., clopidogrel)? Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.			
Has the subject experienced any of the following • clinically-significant gastrointestinal bleeding within 3 months before the first dose of study treatment; the participant must be maintained on a prophylactic regimen for management of an upper GI bleeding event with no evidence of recurrence and/or endoscopic confirmation of resolution of the source of a lower GI bleed? • hemoptysis of ≥0.5 teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment? • any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment?			
Does the subject have a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms? **Note**: if initial QTcF (within 28 days before enrollment) is found to be >500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive			

results for QTcF is ≤500 ms, the subject meets eligibility in this regard.				
Pregnant?	Pregnancy Test Date:			
Radiographic evidence of cavitating pulmonary lesion(s)?				
Does the subject have tumor invading or encasing any major blood vessels?				
Breastfeeding?				
Receiving any other investigational agents?				

Pre Study Evaluations:	**Date Done:**
History and Physical Exam (within 8 days prior to starting drug)	
Height, weight, vital signs, EKG, and performance status (within 8 days prior to starting study drug)	
CBC, Diff, Plts; biochemical profile: albumin, alkaline phosphatase, total bilirubin, BUN, sodium, chloride, bicarbonate, calcium, creatinine, glucose, phosphorus, magnesium, potassium, total protein, SGOT [AST], SGPT [ALT], amylase, lipase, TSH: **Send actual lab results**	
Urinalysis within 8 days prior to starting study drug	
Diagnostic imaging studies (within 28 days prior to starting study drug)	
Pregnancy test within 8 days prior to starting study drug	

DESCRIPTIVE FACTORS:

Primary:		Histology:
Other Chronic Diseases: Y / N (If yes, please explain):		
PRIOR THERAPY (Please specify date, procedure, agent, and dose, response; date of last treatment is required.)		
YES	NO	
		1. **Surgery/Biopsy:**
		2. **Chemotherapy:**
		3. **Radiotherapy**:
		4. **Hormonal Therapy:**
		5. **Immunotherapy**:

Physician's Signature: _____ Date: _____

Printed Name of Physician: _____

To be completed by participating center when registering a patient:
Date Registered with NCI _____/_____/_____
Spoke With: _____
Study ID: _____
Eligibility Checklist Completed By: _____
Assigned CRA / Data Manager: _____

A confirmation of registration will be sent to you by the NCI.

Participant Status Updates Form

Complete form and send via encrypted email to:
NCI Central Registration Office (HOIS) at ncicentralregistration-l@mail.nih.gov
***and* fax or email to the Coordinating Center Research Nurse**
(Fax: 301-451-5625, ashley.bruns@nih.gov)

Patient Information:

First name *Last name* *Middle initial*

*ID number:*_____

*Local Protocol Number (P9284):*_____

Off Study Date (mm/dd/yy): _____

Choose one of the following off-study reasons:

_____ *C: Completed Study*
_____ *L: Lost to follow-up*
_____ *R: Refused Further Treatment*
_____ *T: Toxicity*
_____ *D: Death*
_____ *P: Progressive Disease*
_____ *O: Other*

Death Date: (mm/dd/yy): _____

Choose one or more of the following DOD Sources:

*Social Security Death Index SS#:*_____ *http://ssdi.rootsweb.com/*
*Obituaries Document:*_____ *http://www.legacy.com/washingtonpost/DeathNotices*
*Cause of Death*_____
*Place of Death:*_____
*Family/staff member name notifying DOD:*_____

Registrar:

*Name:*_____
*Work Phone:*_____ *Today's Date***:** _____

Comments:

APPENDIX G: Informed Consent Template for Multicenter

Study Title: A Phase 2 Study of Cabozantinib (XL184), a Dual Inhibitor of MET and VEGFR, in Patients With Metastatic Refractory Soft Tissue Sarcoma

Introduction

We invite you to take part in a research study.
First, we want you to know that:

Taking part in this research is entirely voluntary**.**
You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.
You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with family, friends or your personal physician or other health professional.

Why is this study being done?

We are doing this study to try to develop better treatments for cancer. In this study, the experimental drug **cabozantinib** will be given to you. The purpose of this study is to find out if the drug is effective in a particular type of tumor called soft tissue sarcoma, which is what your doctor has diagnosed you with. We are trying to understand how these drugs work in soft tissue sarcomas. For that, this study will look at how cabozantinib may affect the levels of certain proteins in your tumor.

The use of cabozantinib in soft tissue sarcoma is experimental. **Cabozantinib** works by two mechanisms. Firstly, it acts by blocking the formation of new blood vessels in tumors, a process called angiogenesis. New blood vessels provide oxygen and nutrients to growing cancers, and blocking this process can cause cancer cells or the supporting blood vessels to stop growing. A drug that works by the same mechanism, pazopanib, has already been approved by the FDA for the treatment of patients with sarcoma. In laboratory studies, some drugs that block angiogenesis increase the production of c-MET in tumors, which helps cancer cells adapt to not having enough oxygen, so the tumor can keep growing. **Cabozantinib** also blocks c-MET in tumors. By both these mechanisms the ability of the sarcoma tumor cells to survive may be markedly reduced by the drug.

Although we hope this drug will decrease the size of your tumor, we cannot promise or predict the benefits of the treatment at this time. The drug used in this study has known side effects that will be reviewed with you by your medical team before you sign the consent form.

Why are you being asked to take part in this study?
You are being asked to take part in this research study because you have advanced cancer that has progressed after receiving standard treatment, or for which no effective therapy exists.

Have these drugs been given to other people?
Cabozantinib has been studied in many different cancer types like prostate cancer. So far, more than 1300 patients have received cabozantinib in clinical trials for different types of cancers.

How many people will take part in this study?
Up to 55 patients will take part in this study at 4 centers across the United States.

Description of Research Study
What will happen if you take part in this research study?
Before you begin the study
You will need to have the following examinations, tests, or procedures to find out if you can be in the study. These tests are part of your regular cancer care and should be done by your health care team even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor.

If you decide that you would like to participate in this study, you will be asked to sign this consent form. You will then have the examinations, tests, and procedures listed below done to see if you can take part in the study (this is called the screening/baseline evaluation).

- **Complete medical history.**
- **Physical examination,** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood tests** (requiring about 1 tablespoon of blood in total), which include measurement of your white blood cells, red blood cells, platelets, blood sugar and electrolytes, how your liver and kidneys work, and how well your blood clots.
- **Pregnancy test** in women who are able to become pregnant.
- **Urine tests:** A urine test will be done every 4 weeks to check the level of protein excreted by your kidneys. Depending on the results of blood tests, you may be asked to collect your urine for 24 hours for further testing.
- **EKG** to check your heart.
- **CT scans** (a computerized x-ray examination) of your chest, abdomen, and pelvis to measure your tumor(s). Other imaging tests may be done as needed.
- **Pathology slides:** Before starting on the study, we will request tumor slides or blocks to confirm your diagnosis.

During the study
If you are accepted and choose to take part, you will begin taking the study drug cabozantinib. Cabozantinib is taken by mouth. The study drug will be given in cycles. All cycles are 4 weeks (28 days) long.
Cabozantinib is taken 1 hour before or 2 hours after food. Each day that you take study drug, you will be asked to fill in a diary to show when you took the study drugs, how many pills you took, and report any side effects you may have had.

For some study procedures we will need you to come to the _____[name of center]
You will also have tests performed because you are in the study to see how the study drug is

affecting your body and to find out how your body handles the study drug. This will include imaging studies (for example, CT scans) to find out if your cancer has responded.

We will ask that you come to the _____[name of center] for at least 2 days during the first cycle, and then at the beginning of each cycle after that (less often if you have been on study for more than one year). During the first cycle, you may be admitted for the first 2 days of drug administration to make it easier to perform study test and procedures to see how the drugs are affecting your body. If you develop any side effects, you may be asked to visit more often. Please see the study chart for more details.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit** to ask how you are feeling and to evaluate you with a physical examination at the beginning of each cycle (up to 8 days before the start of each cycle; less often if you have been on study for more than one year).
- **Vital signs and physical examination:** will be performed during the clinic visits.
  We will ask that you buy a blood pressure monitor (the cost of may be reimbursed to you; discuss with your study team) and measure your own blood pressure at home at least once a day (preferably twice a day) throughout the study. You will record the readings in a diary. If your systolic blood pressure (top number) is ever more than 150 or your diastolic blood pressure (bottom number) more than 90, you should re-measure your blood pressure 1 to 4 hours later. If your systolic pressure is still greater than 150 or your diastolic blood pressure is still greater than 90, please contact your study team for instructions. You should also call the research team if you experience any symptoms of high blood pressure, such as chest pain, shortness of breath, headache, blood in the urine, or double vision.
- **Blood tests:** Measurement of your white blood cells, red blood cells and platelets, and measurements of your blood sugar, electrolytes, and how your liver and kidneys work will be done each time you are seen in the outpatient clinic. All of these blood tests combined will require 1-2 tablespoons (20-30 mL) of blood each time.
- **Urine test** to check urine protein will be done during the first cycle and then before you start each new cycle (less often if you have been on study for more than one year). You may need it more frequently if the study doctor thinks it is needed to check for signs of possible damage to your kidneys. Depending on the results of urine tests, you may be asked to collect your urine for 24 hours for further testing.
- **CT scans** or other imaging tests such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done every 2 cycles (about every 8 weeks; every 12 weeks if you have been on study for more than 1 year or every 16 weeks if on study for more than 3 years) while you are receiving treatment. This is done so that any benefit of the treatment can be determined, and so that if your cancer is not responding to the treatment, the study team can tell you and help you move to a different treatment program (discussed further below).

Tests and procedures being done to see how the drug is affecting your body:

- **Research blood samples (optional):** We may collect blood samples to help us find out if cabozantinib affects the levels of certain proteins. Blood will be collected before you first

take the drug and on the first day of cycles 1 and 2 only. Please see the study chart for more details. The total blood for all these tests will be about 2 teaspoons.

- We will also be collecting optional blood samples to find out the effects of the drug on any tumor cells in your blood. Blood samples will be collected before you first take the drug, on the first day of cycle 1, and on the first day of every cycle for as long as you are on study (every 3 cycles if you have been on study for more than one year or every 4 cycles if more than 3 years). Each blood collection is about 2 teaspoons.

Study Chart
The treatment is given over periods called cycles. All cycles are 4 weeks long. Treatment cycles will be repeated as long as you are tolerating the drugs and your cancer is either stable or getting better. Each cycle is numbered in consecutive order. The chart below shows what will happen during Cycle 1 and future cycles. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day. This schedule shows what will happen to you after you sign the consent and start the study.
Cabozantinib should be taken with water at least 1 hour before or 2 hours after a meal. The drug tablets should be swallowed whole with water and may not be crushed or broken.

Day	What to do and what will happen to you
Before starting study drugs	• Check in at _____[name of center] • Get routine blood and urine tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider (can be completed up to 8 days before the start of the study) • CT or MRI scan will be done • EKG will be done • Research blood samples (optional) may be taken
Cycle 1, Day 1	• Admitted to _____[name of center] • Begin taking cabozantinib 60 mg PO by mouth each day • Research blood samples will be taken • You will be asked to keep a record of pill consumption and any new symptoms • Receive study diary
Cycle 1, Day 2-28	• Continue taking cabozantinib by mouth each day
Cycles 2 and 3, Day 1	• Check in at _____[name of center] • Return study diary • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider (can be completed up to 8 days before the start of each new cycle) • Pregnancy test for women who are able to become pregnant • Get routine blood and urine tests (up to 8 days before) • Get a routine EKG (up to 8 days before) • Research blood samples (optional) may be taken

Day	What to do and what will happen to you
	• Continue taking cabozantinib by mouth each day
Cycles 2 and 3, Day 2-28	• Continue taking cabozantinib by mouth each day
Cycle 4 onwards, D1 *Clinic visits on D1 will be every 3 cycles (every 12 weeks) if you have been on study for more than one year or every 4 cycles (every 16 weeks) if you have been on study for more than 3 years*	• Continue taking cabozantinib by mouth each day • Check in at _____[name of center] • Return study diary • Research blood samples (optional) may be taken on the first day of each cycle • Have a history taken of how you feel and undergo a physical examination including vital signs by a Health Care Provider (can be completed up to 8 days before the start of each new cycle) • Pregnancy test for women who are able to become pregnant • Get routine blood and urine tests (up to 8 days before) • EKG tests (up to 8 days before) • CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (every 8 weeks; every 12 weeks if you have been on study for more than one year or every 16 weeks if more than 3 years)

Risks or Discomforts of Participation
What side effects or risks can I expect from being in this study?

If you choose to take part in this study, there is a risk that the XL184 (cabozantinib) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:
- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The XL184 (cabozantinib) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:
- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

High blood pressure is one common side effect of cabozantinib. Your blood pressure will be closely watched while you are taking this drug. You will also be checking your blood pressure at home at least once a day (preferable twice a day) for the entire study. If you have high blood pressure while taking cabozantinib, your study doctor may recommend follow-up with your primary care physician and/or starting or increasing medication to lower your blood pressure.

Some patients on this study have experienced blood clots in the lungs, possibly related to the study drug. Let your doctor know immediately if you experience any shortness of breath or chest pain.

In addition, some patients on this study have experienced sepsis, or an infection in the bloodstream, possibly related to the study drug. This condition can cause fever, increased heart rate, increased breathing rate, and confusion. Sepsis can be life-threatening.

Grapefruit juice has been shown to affect how the body handles some drugs by blocking the activity of the body's cytochrome P450 (CYP450) system. CYP450 is important in breaking down substances in the body, including cabozantinib. 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. We do not know if taking cabozantinib will cause other drugs you may be taking to work differently. **It is very important that you talk to a member of the research team before beginning any new drugs, over-the-counter medications, vitamins, or alternative therapies.**

Risks and side effects related to cabozantinib may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste • Redness, pain or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Infection • Bruising, bleeding • Dehydration • Muscle weakness • Dizziness, headache • Cough, shortness of breath • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Bleeding from multiple sites including the nose • Changes in voice • Hair loss, rash • Change in hair color • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving XL184 (cabozantinib), 3 or fewer may have:
• A tear or hole in internal organs that may require surgery • Non-healing surgical site • Damage to the jawbone which may cause loss of teeth • Bleeding in the brain which may cause confusion • Stroke which may cause paralysis, weakness • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Lung collapse

Reproductive Risks:
If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how cabozantinib would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice **two** effective forms of birth control before starting study treatment, during study treatment, and for 4 months after you finish study treatment. Your study team will talk with you about the kinds of birth control that can be used in this study.
If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [injections, or implants]: estrogen containing pills are not allowed due to the risk of blood clotting

- tubal ligation
- vasectomy

Side Effects of Blood Draw:

Infrequent (occurs in 1 to 10 out of 100 people): persistent pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. You should discuss other treatment options with the study team and your home doctor before deciding to take part in this study. We do know that information from this study will help doctors learn more about these study drugs. This information will also help future cancer patients.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to take part, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution if you are eligible and choose to participate in another trial. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI will supply cabozantinib at no charge while you take part in this study. Even though it is unlikely, there is a possibility that at some point the supply of study agents may run out, necessitating taking you off-study.

[If applicable, inform the patient of any tests, procedures, or agents for which there is no charge. The explanation, when applicable, should clearly state that there are charges resulting from performance of the test or drug administration that will be billed to the patient and/or health plan. For example, "The NCI is supplying (drug) at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug)."]

You will not be paid for taking part in this study.
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Stopping Therapy
Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if too many patients in the study experience severe side effects
- if you become pregnant

In this case, you will be informed of the reason therapy is being stopped. You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.
If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Follow-up

You will be followed for 30 days after taking the last dose of study drug. We will call you after about 30 days to ask about any side effects that were ongoing when you stopped therapy, or any new side effects that might be related to the study therapy. If you have side effects that might be related to the study drugs that have not gotten better after 30 days, we will call you every 2 weeks until the side effects have become stable or gotten better. The follow-up period will end if you enroll on another protocol or start receiving standard therapy.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*
You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records, including research records, for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Qualified representatives from the pharmaceutical collaborator may also review the medical records.
- Designated investigators from other cancer centers participating in this study, including the University of Southern California/Norris Comprehensive Cancer Center; the University of California, Davis, Cancer Center; and Stanford University Medical Center

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to participate, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our center. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.
Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.
For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*
[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Where can I get more information?
You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Use of Specimens and Data for Future Research
To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.
We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

My specimens and data may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____
Date _____

APPENDIX H: PD Collection Worksheets

Date:	PD SAMPLE COLLECTION SHEET: Cycle 1 Day 1				
Protocol: 9284 **Dose level:** **XL184 Dose:** **Patient ID:**		**Ht:** **Wt:** **BSA:**	**Page _____for Sample Pick-up** **Lab phone:**	**Research Nurse:** Phone: Pager: **PI:** Phone:	
Diagnosis/subtype:					
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to drug**	**PD 300** K2 EDTA 3 mL x1 Label tube: sample number, date and time	-----		
Day 1	**Prior to drug**	**PD 400** 6 mL NaHep x1 Label tube: sample number, date and time	------		
Administer XL184, Time:					
Day 1	**3-6 hours post dose**	**PD 301** K2 EDTA 3 mL x1 Label tube: sample number, date and time			
Day 1	**4 hours post dose**	**PD 401** 6 mL NaHep x1 Label tube: sample number, date and time			

Date: **PD SAMPLE COLLECTION SHEET: Cycle 2 Day 1**

Protocol: 9284
Dose level: **XL184 Dose:** **Ht:**
Wt:
Patient ID: **BSA:**

Page _____for Sample Pick-up
Lab phone:

Research Nurse:
Phone: Pager:
PI:
Phone:

Diagnosis/subtype:

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug**	**PD 402** 6 mL NaHep x1 Label tube: sample number, date and time	------		
Administer XL184, Time:					
Day 1	**3-6 hours post dose**	**PD 302** K2 EDTA 3 mL x1 Label tube: sample number, date and time			

Date:	**PD SAMPLE COLLECTION SHEET: Day 1 each cycle/determined by PI**				
Protocol: P9284 **Dose level:** **XL184 Dose:** **Patient ID:**		**Ht:** **Wt:** **BSA:**	**Page _____for Sample Pick-up** **Lab phone:**	**Research Nurse:** Phone: Pager: **PI:** Phone:	
Diagnosis/subtype:					
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to drug**	**PD 40X** 6 mL NaHep x1 Label tube: sample number, date and time	------		
Administer XL184, Time:					