SUMMARY OF CHANGES

Date: January 24, 2014

Document: NCI Protocol #9303, PhII-125: "Phase II Trial of XL184 (Cabozantinib) Plus Erlotinib in Patients with Advanced EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) who have Progressed on Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy."

Note: The following is a Summary of Changes between the 11.5.13 and 1.24.14 versions of protocol

#	Section	Comments
1.	Face page and Protocol Version	Changed protocol version to January 24, 2014. Dates in the headers were also changed to 1.24.14v.
2.	Table of Contents	Updated page numbers in the Table of Contents.
3.	7	References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol.
4.	7.1	Per the Request for Rapid Amendment distributed on 1/7/14, inserted revised CAEPR (Version 2.1, August 26, 2013) for XL184: • Added New Risk: • Also Reported on XL184 Trials But With the Relationship to XL184 Still Undetermined: Alkaline phosphatase increased; Allergic rhinitis; Ataxia; Blurred vision; CPK increased; Cataract; Cheilitis; Colitis; Disseminated intravascular coagulation; Edema face; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Esophageal ulcer; Eye disorders - Other (corneal epithelium defect); Febrile neutropenia; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); GGT increased; Gastric ulcer; General disorders and administration site conditions - Other (implant site inflammation); Hematuria; Hemolytic uremic syndrome; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hyperthyroidism; Hypoalbuminemia; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Investigations - Other (eosinophil count increased); Investigations - Other (glucose urine present); Investigations – Other (urine ketone

#	Section	Comments

		body present); Left ventricular systolic dysfunction; Lymphocyte count decreased; Malaise; Metabolism and nutrition disorders - Other (hypoproteinemia); Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Neck pain; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Nervous system disorders - Other (hemiparesis); Osteoporosis; Pleural effusion; Portal vein thrombosis; Psychiatric disorders - Other (mental status changes); Rectal pain; Renal and urinary disorders - Other (hemorrhage urinary tract); Respiratory, thoracic and mediastinal disorders - Other (rales); Skin ulceration; Stroke; Urinary tract obstruction; Vascular disorders - Other (bleeding varicose vein); Wrist fracture
		
		• Increase in Risk Attribution:
		  • Changed to Likely from Less Likely: Aspartate aminotransferase increased; Dysgeusia; Hypertension; Voice alteration; Vomiting; Weight loss
		  • Changed to Less Likely from Rare But Serious: Thromboembolic event
		  • Changed to Less Likely from Reported But Undetermined: Anemia; Arthralgia; Back pain; Cough; Edema limbs; Hypokalemia; Insomnia; Musculoskeletal and connective tissues disorder – Other (muscle spasms)
		
		• Decrease in Risk Attribution:
		  • Changed to Reported But Undetermined from Less Likely: Investigations - Other (blood lactate dehydrogenase increased); Neutrophil count decreased; Proteinuria; Serum amylase increased; White blood cell decreased
		
		• Provided Further Clarification:
		  • Investigations – other (pancytopenia) is now reported as Blood and lymphatic system disorders - Other (pancytopenia)
		
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: Abdominal pain; Dry mouth; Dry skin; Dyspepsia; Hypothyroidism; Lipase increased; Oral pain; Platelet count decreased; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other

#	Section	Comments
		(hair color changes) • Deleted Risk: • Deleted from Reported But Undetermined: Atrial flutter; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossodynia); Investigations - Other (electrocardiogram ST segment depression); Presyncope; Renal and urinary disorders - Other (Nephrotic syndrome)

NCI Protocol #: 9303

Local Protocol #: PhII-125

TITLE: Phase II Trial of XL184 (Cabozantinib) Plus Erlotinib in Patients with Advanced EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) who have Progressed on Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy

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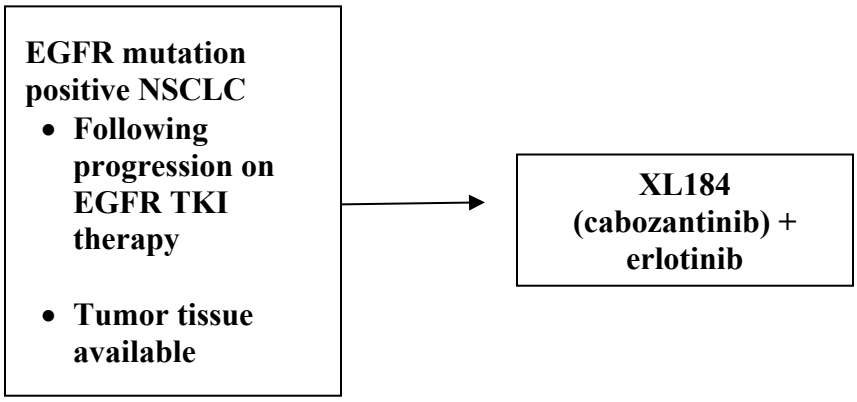
NCI Supplied Agent(s): XL184 (cabozantinib) (NSC 761968; IND 116059)
Erlotinib (NSC 718781; IND # 63383)

IND Sponsor: National Cancer Institute

Protocol Type / Version # / Version Date: October 22, 2012 – Original Protocol
January 3, 2013 – Consensus Review
February 25, 2013 – Follow Up Review
June 17, 2013 – Amendment
October 15, 2013 – Amendment (disapproved)
November 5, 2013 - Amendment
January 24, 2014 _ Request for Rapid Amendment

SCHEMA



This is a phase II trial to evaluate XL184 (cabozantinib) plus erlotinib in patients with advanced NSCLC harboring an EGFR mutation who have progressed following EGFR TKI therapy. Patients may have received prior chemotherapy, and must have progression on erlotinib (retreatment with erlotinib is allowed). Patients will receive cabozantinib at 40 mg p.o. daily plus erlotinib at 150 mg p.o. daily. All subjects will be monitored for clinical and biological responses and toxicity. The cycle length is 28 days. The duration of treatment will continue until subjects develop progressive disease or unacceptable toxicity. The primary endpoint is to determine the response rate of XL184 (cabozantinib) and erlotinib in patients with an EGFR mutation who have progressed on erlotinib.

Archival tissue specimens and serial blood draws will be prospectively collected from all patients. Patients who have an additional biopsy following initial EGFR TKI therapy or after progression on study will have archival tissue collected to identify factors contributing to EGFR resistance (i.e., EGFR T790M mutations, MET amplification). Analysis of ligands, growth factors and soluble receptors will be conducted in serial blood draws from all consenting patients, with an emphasis on baseline levels and changes in VEGF and HGF levels, as well as other ligands that may mediate resistance.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

To evaluate for efficacy by response rate (RR) when patients with advanced non-small cell lung cancer (NSCLC) harboring an EGFR mutation who have progressed following EGFR TKI therapy are treated with XL184 (cabozantinib) and erlotinib.

1.2 Secondary Objectives

1.2.1 Determine PFS for combination XL184 (cabozantinib) and erlotinib in EGFR mutation positive patients following progression on erlotinib.
1.2.2 Assess overall survival.
1.2.3 Evaluate change in tumor growth rate on XL184 (cabozantinib) and erlotinib.
1.2.4 Evaluate type, severity, duration and outcome of toxicities.
1.2.5 Correlate outcome with tumor biomarkers such as MET amplification, T790M mutation, and serum markers of the VEGF and MET pathways in a preliminary manner.

2. BACKGROUND

2.1 EGFR Mutation-Positive NSCLC

The search for improved therapies in NSCLC has led to the investigation of agents that target novel pathways involved in tumor proliferation, invasion, and survival. EGFR signaling activates a pathway that promotes tumor proliferation, migration, stromal invasion, neovascularization, and resistance to apoptosis (Shawver, Slamon et al. 2002). A subgroup of patients with NSCLC that have specific mutations in the EGFR gene that correlate with clinical responsiveness to tyrosine kinase inhibitor therapy (Lynch, Bell et al. 2004; Paez, Janne et al. 2004). These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor, and improved progression-free survival (PFS) when used as first-line therapy in advanced NSCLC (Mok, Wu et al. 2009; Mitsudomi, Morita et al. 2010). Research evaluating which NSCLC patients respond to these agents reveals that the majority of responders have activating mutations in the EGFR gene, approximately 90% of which are deletions in exon 19 or L858R point mutations in exon 21.

However, not all NSCLC patients with EGFR mutations respond to EGFR-targeted therapy, and for those who initially respond to therapy, secondary resistance eventually develops. A specific EGFR mutation, T790M in exon 20, which generally develops after drug treatment is found in approximately 50% of patients with acquired erlotinib resistance (Pao, Miller et al. 2005). It remains unclear whether T790M is the cause of clinical resistance in this entire population. More recently, germline and de novo T790M mutations have been described, with decreased responsiveness to EGFR TKI therapy (Bell, Gore et al. 2005; Tibaldi, Giovannetti et al. 2011; Su, Chen et al. 2012). This data adds evidence that MET and other mechanisms are highly involved in EGFR TKI resistance. Focal amplification of the MET proto-oncogene promotes acquired EGFR TKI resistance in approximately 20% of cases (Bean, Brennan et al. 2007;

Engelman, Zejnullahu et al. 2007; Turke, Zejnullahu et al. 2010). In addition, overexpression of MET by immunohistochemistry may identify a larger group of patients that could respond to MET inhibition. Other mechanisms of resistance in patients with activating EGFR mutations are still unknown. Optimal therapy following progression on EGFR TKI therapy for patients with activating EGFR mutations after standard chemotherapy is not established (Miller, Hirsch et al. 2010), although it has been demonstrated that sensitivity to EGFR inhibition can be regained (Sequist, Waltman et al. 2011). For patients who are not on clinical trial, erlotinib or gefitinib can be re-introduced, but limited data exists on its efficacy in this refractory population of patients (Becker, Crombag et al. 2011).

2.2 XL184 (Cabozantinib)

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

RTKs regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair (Christensen, Burrows et al. 2005). Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers.

The RTK MET, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) (Christensen, Burrows et al. 2005). MET and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's Brochure, 2011). MET-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking MET and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of MET by mutation of gene amplification in multiple cancer types; (4) introduction of MET and HGF (or mutant MET) into cell lines, conferred the properties of tumorigenicity and metastatic propensity on engineered cells; (5) introduction of MET or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of MET or HGF function with dominant-negative receptors, antibody antagonists

(both Met and HGF), and biologic antagonists (*e.g.*, NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo (Christensen, Burrows et al. 2005).

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated MET activity (Liu, Newton et al. 2010), either by means of MET kinase overexpression (Comoglio, Giordano et al. 2008), activating MET gene mutations and/or amplification (Jeffers, Schmidt et al. 1997; Schmidt, Duh et al. 1997; Comoglio, Giordano et al. 2008), or increased autocrine and/or paracrine secretion of the MET ligand, HGF/SF (Birchmeier, Birchmeier et al. 2003; Boccaccio and Comoglio 2006; Comoglio, Giordano et al. 2008). These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of MET has been correlated with poor clinical prognosis (Birchmeier, Birchmeier et al. 2003).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Roskoski 2008). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (Tugues, Koch et al. 2011). High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer and poor survival.

Nonclinical Development of XL184 (cabozantinib)

In Vivo Activity
Inhibition of the VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes, Allen et al. 2009). In RIP-Tag2 transgenic mice, tumors treated with XL184 (cabozantinib) 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 (Sennino, Naylor et al. 2009). All mice treated with XL184 (cabozantinib) (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, Sennino et al. 2011). Tumors were 35% smaller after XL184 (cabozantinib) treatment than corresponding values for vehicle control mice. MET protein expression in tumors was slightly decreased, but phosphorylated 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 (Yakes, Chen et al. 2011). XL184 (cabozantinib) 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 (cabozantinib) disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 (cabozantinib) 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 (cabozantinib) inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of XL184 (cabozantinib) was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both MET and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang, Zhau et al. 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 (cabozantinib) or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2011). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 (cabozantinib) treated animals appeared mostly normal. Thus, XL184 (cabozantinib) treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of XL184 (cabozantinib) and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2010). XL184 (cabozantinib) 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 (cabozantinib). 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 (cabozantinib) resulted in significant inhibition of MET phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2010). Dose-dependent inhibition of phosphorylation of MET and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

MET phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184 (cabozantinib), 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated MET (Yakes, Chen et al. 2011). This effect was reversible, as MET phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy (Investigator's Brochure, 2010). In rats,

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

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2010). In rats, the oral bioavailability of XL184 (cabozantinib) dosed as a solid was approximately 100% of XL184 (cabozantinib) dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single XL184 (cabozantinib) oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) (Investigator's Brochure, 2010). With repeat daily oral dosing in rats, systemic exposure (AUC_{0-t} values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The C_{max} and AUC_{0-t} values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to XL184 (cabozantinib) in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (C_{max} and AUC_{0-t} values) associated with single XL184 (cabozantinib) oral doses in dogs increased less than dose-proportionally with increasing XL184 (cabozantinib) dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption (Investigator's Brochure, 2011). With repeat daily dosing, exposure (C_{max} and AUC_{0-24} values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

<u>Toxicology</u>
In rodents and non-rodents, histopathological changes associated with XL184 (cabozantinib) 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 (cabozantinib) administration. Adverse effects following oral exposure to XL184 (cabozantinib) 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 (cabozantinib) 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 (cabozantinib) capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 (cabozantinib) 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 (Investigator's Brochure, 2010). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184 (cabozantinib)-treated rats or on cardiovascular function in XL184 (cabozantinib)-treated dogs.

Clinical Experience

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

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2012). Safety and efficacy information, from the 2012 Investigator's Brochure, is summarized below.

Phase I Studies

Study **XL184-001** was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd to 11.52mg/kg (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule), and at 175mg qd and 265mg qd (using PIB suspension), and at 175mg qd and 250mg qd (using capsules [25 and/or 100mg]) for two, 14-day cycles were enrolled. The capsule MTD was determined to be 175 mg qd (Kurzrock *et al*., 2011). Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of ≥30%, and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

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

Study **XL184-004** is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules 30 minutes after administration of a high-fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules under fasting conditions). Blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics. See "Pharmacokinetics" section for results.

Study **XL184-005** is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK. See "Pharmacokinetics" section for results.

In Study **XL184-008**, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase 1 study, **CA205-001**, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. A total of 14 subjects in the dose-escalation portion of the study were treated across 3 dosing levels ranging from 50 mg qd to 100 mg qd. The capsule MTD was determined to be 75 mg administered qd. Because of a change in study sponsor, this study was reinitiated as **XL184-014.**

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

Phase 2 Studies

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

Study **XL184-203** was a phase 2 randomized discontinuation trial. Subjects were enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. A total of 526 patients were enrolled in this study . Patients experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including eight fatal related SAEs.

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

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Adverse Events

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

were assessed as related to study treatment with XL184 (cabozantinib) (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

There have been 15 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), PE (two subjects), respiratory failure (two subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (two subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), hemorrhage (presumed to be hemoptysis; one subject), and diverticular perforation, peritonitis (one subject) (Investigator's Brochure, 2011).

Pharmacokinetics

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

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal $t_{1/2,\,z}$ of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for C_{max} and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable time point or to infinity [$AUC_{0\text{-last}}$ or $AUC_{0\text{-inf}}$]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, a high-fat meal did not appear to alter the terminal $t_{1/2,\,z}$ of cabozantinib [mean $t_{1/2,\,z}$: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max} to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the

cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-last}}$ fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib (e.g., chronic use of modafinil) should be avoided because of its potential to reduce cabozantinib exposure. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

2.3 Erlotinib (OSI-774)

Erlotinib (OSI-774 Tarceva®) is an orally active, potent, selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase (Erlotinib Investigator's Brochure, 2012). Erlotinib inhibits the human EGFR tyrosine kinase with a 50% inhibitory concentration (IC50) of 2 nM (0.786 ng/mL) in an *in vitro* enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC50 of 20 nM (7.86 ng/mL). Erlotinib inhibits EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the G1 phase.

Erlotinib appears to bind specifically to EGFR. In a study of erlotinib binding specificity, affinity of erlotinib for 67 cellular receptors was examined (Erlotinib Investigator's Brochure, 2012). Erlotinib was shown to bind with low affinity to peripheral benzodiazepine (IC50=2.5 μM [980 ng/ml]), adenosine A1 (IC50=6.8 μM [2700 ng/ml]), and μ-opiate (IC50=7.0 μM [2800 ng/ml])

receptors. Binding affinities were 1250-fold higher than the IC50 concentration needed to inhibit purified EGFR tyrosine kinase (2 nM [0.79 ng/ml]). When tested at concentrations up to 1 μM (390 ng/ml), no significant inhibition of ligand binding to 64 other neurotransmitter receptors, regulatory binding sites, calcium channels, opioid receptors, or neurotransmitter uptake sites were observed.

Non-Clinical Studies

In mice, daily oral administration of erlotinib for 20 days inhibited subcutaneous (SC) growth of the HN5 human head and neck carcinoma in a dose-dependent manner as compared to vehicle-treated mice, with an estimated effective dose for 50% inhibition (ED50) of 9.2 mg/kg/day (Erlotinib Investigator's Brochure, 2012). Treatment with 11 mg/kg/day of erlotinib immediately halted growth or slightly decreased the size of HN5 tumors >1 cm in diameter. The tumor stasis profile appeared to extend beyond the treatment period such that the tumor size for erlotinib - treated animals did not exceed pretreatment levels until at least 33 days post-treatment. Similar results were observed in A431 squamous cell carcinoma xenografts at a dose of 11 mg/kg/day erlotinib over 20 days.

Erlotinib (10 mg/kg/day) has been studied in combination with cisplatin, doxorubicin, 5-fluorouracil, paclitaxel, vinorelbine tartrate, and gemcitabine (Erlotinib Investigator's Brochure, 2012). No antagonism of therapeutic efficacy was observed, and additive effects were observed with cisplatin (10 mg/kg intravenous [IV] daily × 1), doxorubicin (15 mg/kg IV daily × 1), paclitaxel (10 mg/kg intraperitoneal [IP] daily × 5), and gemcitabine (100 mg/kg IP three times daily × 4).

Nonclinical toxicology studies in rats and dogs have included acute and long-term general toxicology, genetic toxicology, reproductive toxicology, and local tissue tolerance of erlotinib. Clinical signs of toxicity in rats and/or dogs following a single dose of erlotinib were dose dependent and included transient emesis, ataxia, papillary dilation, increased heart rate, decreased blood pressure, decreased activity, irregular respiration, convulsions, rapid chewing, salivation, and death. Following chronic administration in rats and dogs, the following toxicities were observed in at least one species: effects on the cornea (atrophy and ulceration); effects on the skin (follicular degeneration and inflammation, redness, and alopecia); atrophy of the ovary, lacrimal glands, and salivary glands; necrosis of the liver; papillary necrosis and tubular dilatation of the kidney; inflammation in the mandibular lymph nodes; hematopoiesis; delayed gastric emptying; and diarrhea. Increases in alanine aminotransferase, aspartate aminotransferase, and bilirubin were observed.

Erlotinib causes maternal toxicity with associated embryo-fetal lethality and abortion in rabbits at doses 3 times those in humans (AUC at 150 mg daily dose). However, when administered during organogenesis at plasma concentrations approximately equal to humans, no increase in embryo-fetal lethality or abortion in rats or rabbits was observed. Female rats treated with doses 0.3 to 0.7 times the human dose prior to mating and during the first week of gestation had an increase in early resorptions. No teratogenic effects were observed in rats or rabbits.

Pharmacokinetics

The total clearance of erlotinib decreased with increasing dose, resulting in supraproportional increases in exposure (AUC) over the dose range of 1-2 mg/kg IV in rats and 0.5-7 mg/kg IV in dogs (Erlotinib Investigator's Brochure, 2009). *In vitro*, erlotinib is slowly oxidized by liver microsomes. The majority of the absorbed dose is extensively metabolized in rats and dogs, and only a small amount is excreted as unchanged drug in urine, bile, and feces. The oral bioavailability of an aqueous suspension is 77% in rats and ~88% in dogs. Plasma protein binding of erlotinib ranges from 92% to 95% in man, monkey, rat, and mouse, and is 85% in the dog. Corrected for protein binding of 95%, at the average plasma concentration responsible for 50% inhibition of tumor growth (oral dose of 9.2 mg/kg/day in the murine/human tumor xenograft model), the unbound concentration of drug in the plasma is estimated to be 86 nM (34 ng/mL). The estimated unbound concentration of erlotinib in plasma is consistent (4-fold higher) with the IC50 for the *in vitro* cellular phosphotyrosine reduction assay and is 43-fold higher than the IC50 for the *in vitro* (isolated enzyme) tyrosine kinase assay. Finally, Erlotinib plasma protein binding depends on the levels of α-1-acid glycoprotein (AAG). Thus, AAG might be a significant determinant of pharmacokinetic and possibly pharmacokinetic–pharmacodynamic relationships in patients.

Erlotinib pharmacokinetics were examined in patients with advanced solid tumors who were treated daily for 21 days. Plasma samples were collected on Days 1, 3, and 21 for analysis. The following table lists the pharmacokinetic data for these patients:

Mean (%CV) Erlotinib Pharmacokinetic Parameters following Daily Dosing

Dose (mg)	N	AUC_{0-24} (ng·h/ml)			R*		C_{avg} (ng/ml)			C_{max} (ng/ml)		
		Day 1	Day 3	Day 21	Day 3	Day 21	Day 1	Day 3	Day 21	Day 1	Day 3	Day 21
25	3	1580 (40)	2180 (49)		1.38 (11)		66	91		208 (38)	310 (40)	
50	6[a]	5650 (54)	5790 (57)	14900 (69)	1.59 (31)	1.83 (30)	235	241	621	508 (34)	716 (55)	682 (59)
100	8[b]	9210 (92)	9080 (49)	32200 (148)	1.75 (35)	3.21 (56)	384	378	1340	765 (69)	1140 (49)	1740 (85)
150	7[c]	14200 (71)	20600 (22)	45800 (99)	1.74 (6.7)	2.57 (47)	670	859	1910	1040 (70)	2040 (21)	1730 (82)
200	7	36000 (34)		74200 (29)		2.01 (42)	1360		3200	1420 (47)		2910 (29)

Abbreviations: AUC_{0-24}, Area under the time-concentration curve from 0 to 24 hours; C_{avg}, daily average plasma concentration; C_{max}, maximum serum/plasma concentration; CV, coefficient of variance; R, accumulation ratio
*Accumulation ratio = $AUC_{Day\ 3\ or\ 21}/AUC_{Day\ 1}$
[a]Only 3 patients day 3, 3 subjects day 21
[b]Only 2 patients day 3, 3 subjects day 21
[c]Only 6 patients day 21

After oral ingestion, the Erlotinib Cmax values (Tmax) were achieved at a median of 3 hours (range, 2 to 12 hours). Both Cmax and AUC0-24 values were roughly proportional to the erlotinib dose in the range of 25 to 200 mg/d (R2 = 0.33 and 0.46, respectively, on Day 1). Inter-subject variability was moderate at the 150-mg/d dose level, as indicated by coefficient of variation values of 64% for Day 1 AUC0-24 and Cmax.

2.4 Rationale

The discovery of the role of angiogenesis in tumorigenesis and metastasis has paved the way for novel antiangiogenic therapies. The combination of EGFR TKI therapy and vascular endothelial growth factor (VEGF) inhibition was evaluated in the phase III BeTa trial (Herbst, Ansari et al. 2011). Bevacizumab/ erlotinib did not improve overall survival versus placebo/erlotinib, but prolonged PFS and was associated with a higher response rate. Additionally, the MET inhibitor ARQ197 improved outcomes when combined with erlotinib, which may provide a mechanism to overcome EGFR resistance (Sequist, von Pawel et al. 2011). In a recent phase 2 study (XL184-202) combining XL184 (cabozantinib) + erlotinib, PR was seen in 3 patients with prior erlotinib therapy and prolonged SD was demonstrated in a patient with a T790M mutation (9+ months).

Evidence suggests that MET and VEGF are important in NSCLC tumorigenesis and EGFR TKI resistance. Therefore, we hypothesize that treatment with XL184 (cabozantinib) plus erlotinib in EGFR mutation-positive NSCLC following EGFR TKI therapy may allow for tumors to overcome this resistance or restore sensitivity to therapy. This trial will evaluate the combination of XL184 (cabozantinib) with erlotinib in patients with EGFR-mutant NSCLC who have progressed on EGFR TKI therapy. Potential correlative markers will be studied by evaluating HGF in serum, and in a subset of patients; if available, pre-treatment tissue samples will be analyzed for T790M mutation and MET amplification to better understand mechanisms for overcoming resistance in these patients.

2.5 Correlative Studies Background

This study provides an opportunity to evaluate mechanisms of resistance and sensitivity to therapy for these patients. Archival tissue specimens and serial blood draws will be prospectively collected from all patients. Patients will have the opportunity to have an additional biopsy following initial EGFR TKI therapy, and prior to protocol therapy. All patients will have archival tissue collected to identify factors contributing to EGFR resistance (i.e., EGFR T790M mutations, MET amplification). Analysis of ligands, growth factors and soluble receptors will be conducted in serial blood draws from all consenting patients, with an emphasis on baseline levels and changes in VEGF and HGF levels, as well as other ligands that may mediate resistance.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed non-small cell lung cancer harboring an EGFR mutation.
NOTE: EGFR mutational status will be known and assays performed in CLIA certified laboratories will be accepted.

3.1.2 Patients should have tumor tissue available for retrieval. Tissue blocks or unstained slides from the time of original diagnosis are acceptable if repeat biopsy is not indicated. Please see Section 9.0 for preparation and shipping of specimens.

3.1.3 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. See Section 11 for the evaluation of measurable disease.

3.1.4 Patients must have received prior EGFR TKI therapy for metastatic disease and have documented evidence of radiologic disease progression while on EGFR TKI as treatment immediately prior to enrollment. (Patients may have received prior chemotherapy, and retreatment with erlotinib is allowed).

3.1.5 Age ≥18 years on day of consent. Because no dosing or adverse event data are currently available on the use of XL184 (cabozantinib) in combination with erlotinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.6 ECOG performance status ≤1 (Karnofsky ≥60%, see Appendix A).

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 × ULN
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional upper limit of normal
– Lipase	<2.0 x ULN and no radiologic or clinical evidence of pancreatitis
– creatinine	≤1.5 × ULN OR
– creatinine clearance	≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
– hemoglobin	≥9 g/dL
– serum albumin	≥2.8g/dL
– urine protein/creatinine ratio (UPCR)	≤1
– serum phosphorus, calcium, magnesium, and potassium	≥ LLN

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

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

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

3.1.10 Prior to the first patient registration, this study must have institutional review board (IRB) approval. A copy of the IRB approval for each site involved must be given to the Data Coordinating Center at City of Hope.

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

3.2 Exclusion Criteria

3.2.1 The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (*e.g.*, cytokines or antibodies) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.

3.2.2 Prior treatment with XL184 (cabozantinib) or other MET/HGF inhibitor.

3.2.3 The subject has received radiation therapy:

- to the thoracic cavity, abdomen, or pelvis within 2 weeks before the first dose of study treatment, or has ongoing complications, or is without complete recovery and healing from prior radiation therapy

- to bone or brain metastasis within 14 days before the first dose of study treatment
- to any other site(s) within 28 days before the first dose of study treatment.

3.2.4 The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 14 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment. Prior erlotinib is required and does not require a 14-day wash out.

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

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

3.2.7 The subject has a primary brain tumor.

3.2.8 The subject has active brain metastases or epidural disease. Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible. Baseline brain imaging with contrast-enhanced CT or MRI scans for subjects with known brain metastases is required to confirm eligibility.

3.2.9 The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 14 days before the first dose of study treatment.

3.2.10 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.

3.2.11 Strong CYP3A4 inducers and inhibitors should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

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/table.aspx; 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.

3.2.12 The subject has experienced any of the following:

- clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment
- 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 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder or coagulopathy.

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

3.2.15 The subject has tumor in contact with, invading or encasing any major blood vessels.

3.2.16 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.

3.2.17 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 that 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) active infection requiring systemic treatment within 28 days before the first dose of study treatment

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

c) history of organ transplant

d) concurrent uncompensated hypothyroidism or thyroid dysfunction within 14 days before the first dose of study treatment

e) history of major surgery as follows (See Appendix H for definitions):
   i. Major surgery within 8 weeks of the first dose of cabozantinib, with complete wound healing. (Patients with ongoing wound healing or other complications will be excluded)

   ii. Minor surgery within 4 weeks of the first dose of cabozantinib. Pleurx catheter placement within 7 days of the first dose of cabozantinib.

3.2.18 The subject is unable to swallow tablets.

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

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

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

3.2.22 History of allergic reactions attributed to compounds of similar chemical or biologic composition to XL184 (cabozantinib) or erlotinib.

3.2.23 Pregnant women are excluded from this study because XL184 (cabozantinib) is a tyrosine kinase inhibitor with 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 XL184 (cabozantinib), breastfeeding should be discontinued if the mother is treated with XL184 (cabozantinib). These potential risks may also apply to other agents used in this study.

3.2.24 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with XL184 (cabozantinib). In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

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

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	3	1	4
Not Hispanic or Latino	17	16	33
Ethnic Category: Total of all subjects	20	17	37
Racial Category			

American Indian or Alaskan Native	0	0	0
Asian	4	4	8
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	15	12	27
Racial Category: Total of all subjects	20	17	37

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the California Cancer Consortium Data Coordinating Center (DCC) at the City of Hope. All sites should call the DCC at (626) 256-4673 extension 65928.

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The DCC should be notified of cancellations as soon as possible.

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.

4.2 Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the data coordinating center a patient will be entered on study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the Consortium office (Data Coordinating Center for the California Cancer Consortium) at the City of Hope (626-256-4673, ext. 65928), email a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form. (email cccp@coh.org). See Appendix E ("Registration Procedures").

The research nurse or data manager at the participating site will then call the Data

Coordinating Center at Tel# 626-256-4673 extension 65928 to confirm receipt of all registration documents. To complete the registration process, the data coordinating center coordinator will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number
- Fax or e-mail the patient study number and dose to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

Following registration, patients should begin protocol treatment within 5 days to allow for drug shipment via Priority Mail. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Data Coordinating Center should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Patients will receive (A) XL184 (cabozantinib) at 40-mg p.o. daily plus erlotinib at 150-mg p.o. daily in 4-week cycles as in Table 1. Cabozantinib and erlotinib may be taken at the same time on an empty stomach. Reported adverse events and potential risks for XL184 (cabozantinib) and erlotinib are described in Section 7. Appropriate dose modifications for cabozantinib and erlotinib 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.

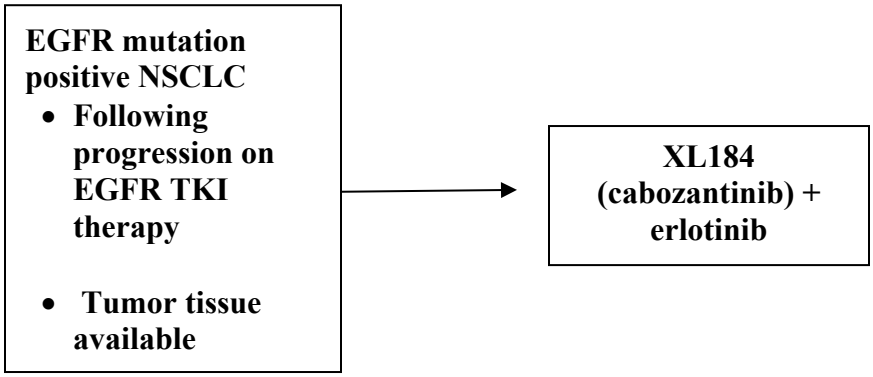


Table 5-1—Dosing Instructions

Regimen Description					
Agent	**Premedications; Precautions**	**Dose***	**Route**	**Schedule**	**Cycle Length**
XL184 (cabozantinib) (Tablet)	Take on an empty stomach without eating for 2 hours before and 1 hour following each dose of XL184 (cabozantinib).	40-mg	oral	Continuous daily	28 days (4 weeks)
Erlotinib (Tablet)	Take on an empty stomach without eating for 2 hours before and 1 hour following each dose of erlotinib.	150-mg	oral	Continuous daily	
* Starting dose, see Tables 6-1 and 6-2 for dose modifications					

The patient will be requested to maintain a medication diary (see Appendix D) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. Patients will be instructed to record doses as they take them (and not to batch entries at a later time) and how to correct errors if they occur.

5.1.1 XL184 (cabozantinib)

XL184 (cabozantinib) must be taken on an empty stomach without eating 2 hours before through 1 hour after taking XL184 (cabozantinib).

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

- Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)
- Do not ingest foods or nutritional supplements (e.g., grapefruit, grapefruit juice, Seville oranges or products made with grapefruit or Seville oranges) that are known to inhibit cytochrome P450.
- Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital).
- Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity.

- Cabozantinib should be taken at approximately the same time each day. If a dose is missed and it is less than 12 hours till the next dose, the missed dose should not be taken. The next dose should be taken at the normal time.
- Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Medications that are highly protein bound (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution during cabozantinib treatment. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.
- 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. Some 5-HT3 antagonist agents (e.g. odansetron, granisetron) can prolong the QTc and should be used with caution. Alternative medications for nausea and vomiting should be used when possible.

5.1.2 Erlotinib

Erlotinib must be taken on an empty stomach. Patients must fast for 2 hours before and 1 hour following each dose of erlotinib.

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

Patients should wear sun screen protection, hat, and long sleeves to avoid sun as it can exacerbate skin rash.

There is a potential interaction between erlotinib and warfarin. Patients have experienced elevated international normalized ratios (INRs) and bleeding with this combination of drugs. Patients on warfarin and erlotinib should have more frequent INR/prothrombin time (PT) determinations.

Proton pump inhibitor: Erlotinib's solubility decreases as the pH increases. Coadministration of omeprazole with erlotinib will decrease the AUC and C_{max} by 46% and 61%, respectively. Caution must be observed when administering erlotinib with omeprazole.

H2-antagonist: Avoid concomitant use of erlotinib with gastric acid-reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H2-antagonist receptor is needed, **take erlotinib at least 2 hours before or 10 hours following the H2-antagonist**

administration. Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

Smoking: Advise smokers to stop smoking while taking erlotinib. Smoking induces CYP1A2 enzymes and alters erlotinib exposure by 64%.

Food-drug interaction: Avoid grapefruit /grapefruit juice (potent CYP3A4) while taking erlotinib.

5.1.3 Other Modality(ies) or Procedures

N/A

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of XL184 (cabozantinib) and erlotinib 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 Concomitant Medications and Therapies

5.2.1.1 Anticancer Therapy

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

5.2.1.2 Other Medications

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

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

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are

acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically prior to the first dose of study treatment.

No concurrent investigational agents are permitted.

5.2.1.3 Potential Drug Interactions

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

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from *in vitro* studies using CYP-isozyme specific neutralizing antibodies.

Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib (*e.g.*, chronic use of modafinil) should be avoided because of its potential to reduce cabozantinib exposure. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (*e.g.*, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may

increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and inducers should be avoided, and CYP3A4 inhibitors and inducers that are not strong, should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

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

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

Protein Binding: Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (*e.g.*, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Drugs Associated with QTc Prolongation: Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs. Some 5-HT3 antagonist agents (e.g. odansetron, granisetron) can prolong the QTc and should be used with caution. Alternative medications for nausea and vomiting should be used when possible.

Other Interactions: In a relative bioavailability study in dogs, cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors (PPIs) and H2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs and H2-antagonists may decrease cabozantinib plasma exposure levels and its effectiveness *in vivo*, resulting in clinically significant drug interactions. The use of

PPIs (*e.g.*, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (*e.g.*, ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H_2 blockers is preferred over PPIs (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib). Antacids, H_2 blockers, or PPIs should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure for XL184 (cabozantinib).

5.3 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Necessity for treatment with other anticancer treatment prohibited by the protocol,
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (*e.g.,* male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment,
- Women who become pregnant or are breast feeding,
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol, or
- Significant noncompliance with the protocol schedule in the opinion of the investigator.

- The minimum dose of study treatment will be 20 mg XL184 (cabozantinib) qod and 50 mg erlotinib qd. Subjects who cannot tolerate 20 mg XL184 (cabozantinib) qod and 50 mg erlotinib qd will have study treatment discontinued.

5.4 Duration of Follow Up

Patients will be followed every 12 weeks for one year and then annually after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

A window of +/- 3 days is allowed for the start of cycles following cycle 1. Patients will be withdrawn from study if they fail to recover to CTCAE grade 0-2 (or within one grade of starting value for pre-existing laboratory abnormalities) from a treatment-related toxicity within 6 weeks (leading to treatment delay of >6 weeks due to AEs).

Table 6-1 Dose Modifications for XL184 (cabozantinib)

Dose Level	XL184 (cabozantinib) Dose
0 (Starting dose)	**40mg daily**
-1	**20mg daily**
-2	**20mg every other day**
Dose reductions will occur for toxicity attributed to the offending agent. If toxicity is related to both agents, both will require dose reduction. All dose reductions are permanent. In situations where the toxicity is attributable to the combination of agents requiring a dose reduction beyond dose level -2, then both agents will be discontinued and the patient will be removed from protocol therapy.	

Table 6-2 Dose Modifications for Erlotinib

Dose Level	Erlotinib Dose
0 (Starting dose)	**150mg**
-1	**100mg**
-2	**50mg**
Dose reductions will occur for toxicity attributed to the offending agent. If toxicity is related to both agents, both will require dose reduction. All dose reductions are permanent. In situations where the toxicity is attributable to the combination of agents requiring a dose reduction beyond dose level -2, then both agents will be discontinued	

and the patient will be removed from protocol therapy.

XL184 (cabozantinib)-Related Adverse Event Management

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

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Tables 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-9, and 6-10. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinurea, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate section below. Guidance for the management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Cabozantinib Investigator's Brochure.

Table 6-3. General Approach to the Management of XL184 (cabozantinib)-Related Non-Hematologic Adverse Events

CTCAE Version 4 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 one level • 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 which is easily managed by medical intervention or resolved quickly	• 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 dose reduction by one level 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 by one level 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 one level 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 by one level with discussion with the PI.
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 6-4. General Approach to the Management of XL184 (cabozantinib)-Related Hematologic Adverse Events

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤1, and resume cabozantinib treatment at a reduced dose by one level.
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 by one level.
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 by one level.
Grade 4 febrile neutropenia	Permanently discontinue study treatment.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment.
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).

Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

Diarrhea

Patients should be instructed to use loperamide for the prevention of diarrhea and initiate upon the first loose stool (4mg at first onset, followed by 2mg every 2-4 hours until diarrhea resolves for 12 hours). Patients should notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson, Ajani et al. 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1 and 6-3 should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1 and 6-3 should be followed.

Some 5-HT3 antagonist agents (e.g. odansetron, granisetron) can prolong the QTc and should be used with caution. Alternative medications for nausea and vomiting should be used when possible. 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.

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.

Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases. Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Table 6-5. General Approach to the Management of XL184 (cabozantinib)-Related Transaminase Adverse Events

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks.. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1.

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 $< 1.5 \times$ ULN, total bilirubin $< 1.5 \times$ ULN, aminotransferases $\leq$ 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.

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.

Table 6-6. 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 ≤2 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose by one level provided that this occurs within 6 weeks. •
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤2 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose by one level. If resolution took more than 4 days, the dose must be reduced by one level upon retreatment provided that resolution occurred within 6 weeks. •

Table 6-7. 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 by one level if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment.

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.

Table 6-8 Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens.
Grade 2	If tolerable, continue cabozantinib at current dose. If intolerable, reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. If treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a treatment interruption is again required, the dose must be reduced when treatment resumes. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, proceed to the management guidelines for Grade 3 PPE.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

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

Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment.. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although

routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

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

Hypertension

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

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (see next Table below).

Table 6-9. Management of Hypertension Related to XL184 (cabozantinib)

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

Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be

discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in the next Table below.

Table 6-10. Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week. If UPCR is < 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1.5, restart cabozantinib at a reduced dose by one dose level. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

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.

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

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors 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.

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.

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.

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.

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.

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.

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

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

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org).
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status *e.g.*, severe or prolonged diarrhea.

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

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not

less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

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

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

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

Erlotinib-Related Adverse Event Management

Table 6-11. General Approach to the Management of Erlotinib-Related Adverse Events

Toxicity	Grade	Dose Modification[1]	Guideline for management
Keratitis	1	None	No intervention
	2 (≤ 14 days)	None	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated with follow-up examination within 2 weeks.
	2 (≥ 14 days)	Hold until recovery to ≤ grade 1, and then reduce 1 dose level	
	≥3	Hold until recovery to ≤ grade 1, and then reduce 1 dose level	
Diarrhea	1	None	Loperamide (4mg at first onset, followed by 2mg every 2-4 hours until diarrhea resolves for 12 hours)[2]
	2	• None if tolerable • If intolerable, hold until recovery to ≤ grade 1, and then resume at the same dose level • If intolerable grade 2 recurs after resumption, hold until recovery to ≤ grade 1, and then reduce 1 dose level	Loperamide (4mg at first onset, followed by 2mg every 2-4 hours until diarrhea resolves for 12 hours)[2]
	≥3 (despite optimal loperamide use)	Hold until recovery to ≤ grade 1, and then reduce 1 dose level[1]	

Rash	1	None	No intervention
	2	• None if tolerable • If intolerable, hold until recovery to ≤ grade 1, and then resume at the same dose level • If intolerable grade 2 recurs after resumption, hold until recovery to ≤ grade 1, and then reduce 1 dose level[1]	Any of the following: minocycline, doxycycline, topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course, ≤ 1 week)
	≥3	Hold until recovery to ≤ grade 1, and then reduce 1 dose level	
Bilirubin	≥3 x ULN	Hold until recovery to ≤ grade 2, and then reduce 1 dose level	No intervention
Liver Transaminases	≥5 x ULN	Hold until recovery to ≤ grade 2, and then reduce 1 dose level	No intervention
Signs and symptoms of interstitial pneumonitis		Any grade; Hold erlotinib pending diagnosis. Permanently discontinue if diagnosis is confirmed and considered possibly related to erlotinib.	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated.
Other toxicity	≥2 prolonged clinically significant toxicity (≥ 1 week)	Hold until recovery to ≤ grade 2, and then reduce 1 dose level	Treatment as clinically indicated
[1]If the dose has previously been held for grade 2 rash or diarrhea and grade 2 symptoms recur, OR if the patients finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level. [2]Loperamide is recommended at the first onset of loose stools.			

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(s) (CAEPRs)

The Comprehensive Adverse Event 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 of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-

specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. 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.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for XL184 (cabozantinib)

Below is the CAEPR for XL184 (cabozantinib). Frequency is provided based on 1345 patients.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cabozantinib (XL184 (cabozantinib), NSC 761968)

Version 2.1, August 26, 2013[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib s-malate) (CTCAE 4.0 Term) [n= 1345]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 2)***

Nausea			***Nausea (Gr 2)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Lipase increased		***Lipase increased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
Weight loss			***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		

		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Respiratory fistula[6]	
	Respiratory hemorrhage[7]		
	Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)		
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (hair color changes)		***Skin and subcutaneous tissue disorders - Other (hair color changes) (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 2)***
	Thromboembolic event[8]		

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

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

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

Also reported on XL184 (Cabozantinib s-malate) trials but with the relationship to XL184 (Cabozantinib s-malate) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Acute coronary syndrome; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Endocrine disorders - Other (thyroiditis); Hyperthyroidism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal ulcer; Cheilitis; Colitis; Duodenal ulcer; Dysphagia; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Hemorrhoids; Ileus; Pancreatitis; Rectal pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (implant site inflammation); Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatitis toxic); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - 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; CPK increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (eosinophil count increased); Investigations - Other (glucose urine present); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myalgia; Neck pain; Osteoporosis
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); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Ataxia; Dysarthria; Dysesthesia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Hypoxia; Laryngeal edema; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pneumothorax; 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)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash acneiform; Skin and subcutaneous tissue disorders - Other (psoriasis); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Vascular disorders - Other (bleeding varicose vein)

Note: XL184 (Cabozantinib s-malate) 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.

7.1.1.2 CAEPR for Erlotinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Erlotinib (OSI-774, NSC 718781)

The Comprehensive Adverse Event 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 , JulyReporting (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 via CTEP-AERS (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 3622 patients.* Below is the CAEPR for OSI-774 (erlotinib).

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, July 24, 2013[1]

Adverse Events with Possible Relationship to OSI-774 (erlotinib) (CTCAE 4.0 Term) [n= 3622]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Eye disorders - Other (corneal perforation)	
		Keratitis	

GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection[4]		***Skin infection[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
	Pneumonitis		***Pneumonitis (Gr 3)***

SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail loss		***Nail loss (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

[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 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.

[3]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.

[4]Includes infection of the skin (folliculitis or cellulitis) as complications of rash.

Also reported on OSI-774 (erlotinib) trials but with the relationship to OSI-774 (erlotinib) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation
EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
HEPATOBILIARY DISORDERS - Cholecystitis
INVESTIGATIONS - Creatinine increased; INR increased (in patients taking Coumadin);

Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Dizziness; Ischemia cerebrovascular; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Thromboembolic event

Note: OSI-774 (erlotinib) 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.

Note: OSI-774 (erlotinib)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of OSI-774 (erlotinib) in patients with baseline hepatic impairment.

7.2 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 for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 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 7.3.4.

- **Attribution** of the AE:

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

7.3 Expedited Adverse Event Reporting

For protocols with CAEPRs not including a "SPEER" category, protocol-specific exceptions to the CTEP-AERS reporting table can be found in the CAEPR's "ASAEL" category instead. This protocol-specific exception is limited to Grade 1 and Grade 2 ASAEL events, i.e. Grade 3 through Grade 5 ASAEL-listed events are NOT exceptions to CTEP-AERS reporting

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

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

7.3.2 Multi-institutional studies
CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

PLEASE INCLUDE CCCP@COH.ORG ON ALL CTEP-AERS REPORTS SUBMITTED.

7.3.3 Expedited Reporting Guidelines

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

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

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

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

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

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

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

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

7.5 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.

7.6 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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with XL 184 and Erlotinib administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 XL184 (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: cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

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

Mode of Action:
XL184 (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:
XL184 (cabozantinib) - NSC 761968 - will be provided free of charge by Exelixis and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

XL184 (cabozantinib) 20 mg will be supplied as tablets for oral administration. The XL184 (cabozantinib) tablets contain XL184 (cabozantinib), microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The Opadry Yellow film coating on the tablet contains HPMC 2910 /hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow.

XL184 (cabozantinib) will be supplied in bottles containing 30 – 20 mg tablets of XL184 (cabozantinib) with a child-resistant cap and tamper evident seal. Dispense XL184 in its original bottle; however, XL184 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.

Administration:
Take XL184 (cabozantinib) on an empty stomach, do not eat 2 hours before through 1 hour after. Do not crush or chew.

Stability:

Stability testing of the intact bottles is on-going. XL184 (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.

Potential Drug Interactions:

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

In vitro data indicate that XL184 (cabozantinib) is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

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

Avoid concomitant use of XL184 (cabozantinib) with proton pump inhibitors (PPIs) and H_2 –antagonists, if possible. The PPIs and H_2–antagonists may decrease XL184 (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 XL184 (cabozantinib). If needed, antacids are recommended for the initial treatment of dyspepsia or indigestion. If antacids are not adequate, the use of H2 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 XL184 (cabozantinib) but at least 14 hours before the next dose of XL184 (cabozantinib) if possible.

Potential Food Effect:

The effect of food on the bioavailability of XL184 (cabozantinib) was evaluated in healthy adult subjects in a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover study (Study XL184-004). Based on the preliminary PK data, a high fat meal did not appear to alter the terminal t1/2, but significantly

increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the XL184 (cabozantinib) Cmax and AUC values by 41% and 57%, respectively. Based on this result, XL184 (cabozantinib) should be taken on an empty stomach [fasting is required 2 hours before and 1 hour after each XL184 (cabozantinib) dose].

Patient Care Implications:

Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. There are many H2-blockers and PPIs available over-the-counter (OTC) such as cimetidine or omeprazole. For dyspepsia or indigestion, use an antacid first, then an H2 blocker if not relief with an antacid. Do not use cimetidine. Take an antacid, an H2 blocker, or a PPI at least 2 hours (preferably 4 hours) after taking XL184 (cabozantinib) but at least 14 hours before the next dose of XL184 (cabozantinib) if possible.

Drug Returns:

Only undispensed drug supplies (no partial bottles) should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when expired supplies are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Transfers:

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2 Erlotinib/OSI-774 (718781)

Chemical Name:	N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride
Other Names:	Erlotinib hydrochloride, Tarceva™
Classification:	Tyrosine kinase Inhibitor (EGFR)
Molecular Formula:	$C_{22}H_{23}N_3O_4$ HCl
M.W.:	393.4 (free base) 429.9 (hydrochloride salt)
Mode of Action:	Direct inhibition of EGFR tyrosine kinase
How Supplied:	Erlotinib tablets are provided by Astellas Pharmaceuticals and distributed by the DCTD/NCI as 25 mg, 100 mg, and 150 mg

white film-coated immediate-release tablets packaged in high-density polyethylene (HDPE) bottle. Each bottle contains 30 tablets.

The tablets are round and convex without markings. The 25 mg tablets are 1/4 inches (6 mm); the 100 mg tablets are 11/32 inches (9 mm); and the 150 mg tablets are 13/32 inches (10 mm). OSI-774 excipients include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Storage: Store the intact HDPE bottles as per label's instruction.

Stability: Current data indicates erlotinib is stable for at least 3 years at room temperature.

Route of Administration: Oral.

Method of Administration:

- Tablets should be taken once daily preferably in the morning with up to 200 mL of water on an empty stomach 2 hours before through 1 hour after.

Potential Drug Interaction: Erlotinib is highly protein bound (92% to 95% in humans) and metabolizes primarily via CYP3A4 enzymes. Dose OSI-774 cautiously with agents that are highly protein bound or potent CYP3A4 inhibitors/inducers enzymes.

CYP Iso-Enzymes Inhibitors/Inducers:

- Potent CYP3A4 Inhibitors: Use alternative drug. Alternatively, reduce erlotinib dose in the event of drug interaction (if permitted by the protocol).
- Potent CYP3A4 inducers: Use alternative drug. If an alternative treatment is contraindicated, consider increasing the erlotinib dose (if permitted by the protocol).
- Food-drug interaction: Avoid grapefruit /grapefruit juice (potent CYP3A4) while taking erlotinib.
- Smoking: Advise smokers to stop smoking while taking erlotinib. Smoking induces CYP1A2 enzymes and alters erlotinib exposure by 64%.

Anticoagulant: Concomitant NSAIDs, warfarin or warfarin-derivatives may increase bleeding and PT /INR. Dose adjustment may be needed.

Proton Pump Inhibitor: Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with erlotinib will increase the AUC and C_{max} by 46% and 61%, respectively.

H_2-antagonist: Avoid concomitant use of erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H_2-antagonist receptor is needed, **take OSI-774 at least 2 hours before or 10 hours following the H_2-antagonist administration.** Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

Gastrointestinal perforation: Concomitant use of anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or patients with prior medical history with peptic ulcers or diverticular disease are at high risk of GI perforation while on erlotinib treatment. Discontinue erlotinib if GI perforation manifests.

Patient Care Implications: If patient vomits after taking the tablets, readminister the dose only if the tablets can actually be seen and counted.
Recommend patients to use sunscreen protection, and wear hat and long sleeve shirts as sunlight can exacerbate skin reactions.

8.1.3 Agent Ordering and Agent Accountability

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

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

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Archival tissue specimens will be collected per eligibility criterion 3.1.2. Serial blood draws are required and will be prospectively collected from consenting patients. Patients who have an additional biopsy following initial EGFR TKI therapy or after progression on study will have tissue collected to identify factors contributing to EGFR resistance (i.e., EGFR T790M mutations, MET amplification). Analysis of ligands, growth factors and soluble receptors will be conducted in serial blood draws from all consenting patients.

Tumor specimens:

1. For all patients, tumor positivity for EGFR will have been established prior to enrollment as routine management. If a post-progression re-biopsy is available, continued EGFR mutation status as well as emergence of the T790M resistance mutation will be determined.
2. Each specimen will be evaluated for MET amplification.
3. Given sufficient tumor specimen, each sample will be evaluated in the following priority order for a) for EGFR IHC expression using the established H-score system, b) the presence of PI3K mutations (particularly exon 20) and c) tumor RNA expression levels of EGFR and MET amplification as determined through Response Genetics Inc.

In post-progression tumor specimens*

If a biopsy was conducted at the time of progression on the prior EGFR inhibitor therapy (presumably erlotinib), then the following will be conducted in available archival specimens:

1. MET copy number abnormalities/amplification by FISH.
2. IHC evaluation of HGF as a paracrine or autocrine stimulator.

*These assays will also be performed in the original diagnostic specimen for patients who have a complete or near complete response to therapy

Analysis of serial plasma specimens

l) A principle goal for analysis of serial patient plasma will be to quantitate baseline levels and treatment-induced changes in the MET ligand HGF. Additionally, through multiplex analysis, ErbB family ligands, including amphiregulin, epiregulin, EGFR and TGF-alpha will be evaluated.

2) Patient plasma will be monitored for the presence of the T790M EGFR mutation in circulating cell-free tumor DNA using previously established techniques (Mack ref). Detection of the original activating mutation (e.g. E19del or L858R) will also be performed. The ratio of

mutant DNA (EGFR E19del, L858R and T790M) to wild-type DNA detectable in plasma will be correlated with tumor burden over time. In responding patients, we expect a decrease in detection of EGFR mutations in peripheral circulation concomitant with decreased tumor burden. Progression would be associated with increased levels, potentially including emergence of the T790M mutation.

9.1.1. EGFR and MET tissue analysis

9.1.1.1. Collection of Specimens

Archival tumor specimens (ideally 1-2 paraffin-embedded tissue blocks containing formalin-fixed tumor from the time of diagnosis, or subsequent to, but prior to therapy) should be submitted for subsequent evaluation of expression and mutation analysis in relevant molecular pathways. Paraffin blocks may be processed according to standard institutional protocols. If blocks are unavailable, 10-15 unstained slides will be accepted as an alternative.

9.1.1.2. Shipping of Specimens

All archival paraffin block/slide specimens should be sent at ambient temperature. Specimens should be shipped to the following address:

Philip C. Mack, PhD
UC Davis Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817

Laboratory Phone: 916-734-3734
Fax: 916-734-2361
Email: philip.mack@ucdmc.ucdavis.edu

A Specimen Submission Form (Appendix F) and a Pathology Report corresponding to the submitted block/slides must be submitted with each specimen. Institutions should notify the recipient by either phone or fax prior to shipping specimens.

9.1.2 DNA and Protein analysis of plasma

9.1.2.1. Collection of Specimens
Molecular Correlative sampling will be conducted at baseline, prior to all subsequent treatment cycles, and when the patient comes off of the study for any reason (see study calendar). It is important that blood is collected at all time points and that the specimens are consistently processed according to protocol instructions.

9.1.2.2. Handling of Specimens

One purple top blood tube (EDTA tubes), ~ 10 ml, should be collected from patients at baseline, prior to all subsequent treatment cycles, and when the patient comes off of the study for any reason. Tube should be spun in a standard laboratory centrifuge at 800 x G for 10 minutes to separate plasma, buffy coat cells, and red blood cells **(see Appendix G for blood handling protocol)**. Plasma should be carefully removed in aliquots of 1 mL each to labeled cryovials. Similarly, the white blood cell buffy coat should be removed and placed in labeled cryovials. All tubes should be frozen as rapidly as possible, and then stored in a -70° C freezer until shipped.

9.1.2.3. Shipping of Specimens

Specimens should be batched on site. At completion, all specimens for a single patient should be shipped **frozen on dry ice** by overnight carrier **Monday through Wednesday only**. A completed specimen submission form (Appendix F) **for each time point** should accompany the shipment.

Shipping Information:
Philip C. Mack, Ph.D.
Division of Hematology/Oncology
University of California, Davis Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817

The Federal Guidelines for Shipment are as follows:

1. The specimen must be wrapped in an adsorbent material;

2. The specimen must be placed in an AIRTIGHT container (resealable bag);

3. Pack the resealable bag and specimen in a Styrofoam shipping container along with enough dry ice to last for 2 days;

4. Pack the Styrofoam shipping container in a cardboard box;

5. The cardboard box must be labeled with a Hazardous Materials label for the Dry Ice.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

The following schedule of assessments applies to all subjects (Table 10-1). More frequent assessments should be obtained if clinically indicated.

Table 10-1. Schedule of Assessments

	Study Treatment Period			Post-Treatment Period
	Within 28 days Prior to 1st Dose of Study Treatment	**Within 14 days prior to the first dose of Study Treatment**	**Day 1 of Weeks 3, 5, 7, 9, 11, and 13 then every 4 weeks (± 3 days)**	**30 - 37 Days after last dose**
Informed consent	X			
Demographics	X			
Medical and cancer history	X			
Physical examination		X	X	X
Height	X			
Weight		X	X	X
Vital signs		X	X	X
ECOG performance status		X	X	X
Clinical laboratory tests[1]		X	X	X
Urinalysis and UPCR		X	X	X
PT/INR, PTT		X	X[2]	
TFTs (TSH, free T3, free T4)		X	X[2]	
12-lead ECG		X	X[2]	X
XL184 (Cabozantinib) administration			X (daily)[3]	
Erlotinib administration			X (daily)	
Pregnancy test (serum)[4]	X[4]		X (every 8 weeks on study)[4]	X
Radiologic evaluation	X		X (performed every 2 cycles; see section 11.1)	
Tumor assessment[5]	X		X (performed every 2 cycles)	
Tumor specimen[6]	X			X[7]
Blood for correlative studies[8]		X	X (every 4 weeks, at start of cycle)	X
Concomitant medications			X	X
Adverse events	Continuous			X

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

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

[2]Done at week 4 then every 8 weeks. Additional ECGs performed as clinically indicated.

[3]Every other day dosing is allowed for dose modification, see Table 6-1.

[4]Women of childbearing potential, within 14 days of study entry. To be repeated every 8 weeks while on study treatment.

[5]All sites of known disease must be assessed.
[6]See section 9 and Appendix G for details.
[7]Optional: See section 9 and Appendix G for details. Post-treatment sample obtained for clinical indications will be collected as available within 6 months of study discontinuation.
[8]Blood samples are to be obtained prior to treatment on the first day of each cycle and when the patient goes off study. See section 9 and Appendix G for details.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response after cycle 1 (4 weeks) and then every 2 cycles (8 weeks). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

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) (Eisenhauer, Therasse et al. 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 XL184 (cabozantinib) and erlotinib.

Evaluable for objective response. Patients who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

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).

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.

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT

scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

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

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

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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.4.3 Evaluation of Best Overall Response

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

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

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

PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

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

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. 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). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

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.

12.1.3 Data Collection Forms and Submission Schedule

All data will be collected using COH data collection forms via an electronic data capture system. Any original data collection forms will reside at the originating institutions in secure location.

ELIGIBILITY CHECKLIST: The data manager at the registering site will have completed and faxed this form at the time of registration.
ON-STUDY FORM (FORM OS): Completed on-study forms due within two weeks of registration.
TREATMENT FORM (FORM RX): Completed treatment forms are due within four weeks of completion of a cycle.
ADVERSE EVENT COLLECTION: Completed adverse events collection form due within four weeks of completion of a cycle.
FLOW SHEETS: Protocol specific flow sheets are to be submitted along with each treatment form.

RESPONSE/OFF-STUDY/FOLLOW-UP: Form F/U is to be submitted each time a patient is evaluated for response and/or new follow-up information is obtained.
SUPPLEMENTAL DATA FORM: The timeline for submission of the supplemental data form will be protocol specific, if applicable.

12.2 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 B.

- 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.

12.3 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

Design: Simon's optimal two-stage design is used.

Primary endpoint: Objective response defined by RECIST.

13.2 Sample Size/Accrual Rate

Enrollment will be done in two stages. In the first stage, 12 patients will be treated. If no patients exhibit a RECIST objective response, enrollment will be closed, unless the tumor growth rate (see secondary objective) provides sufficient evidence to proceed upon consultation with CTEP and the PI. Otherwise, if 1 or more patients have an objective response, the study will continue enrollment to the final sample size of 37 subjects. If 4 or more of the 37 patients respond, the trial will be regarded as indicating adequate activity in tumors with EGFR-mutations, providing other factors, such as toxicity and time to progression, also appear favorable. The probability of indicating activity by this criterion is no more than 0.10 if the underlying response rate is 5%, and it is at least 0.90 if the underlying response rate is 20%.

13.3 Analysis of Secondary Endpoints

1. Studies on targeted agents in a refractory patient population presents unique challenges in design: (1) publications from 1975 [Band and Kocandrle, 1975] and as recent as June 2011 [Tourneau, et al, abstract #2603, ASCO 2011] suggest that therapy should *not necessarily* be stopped upon documented progression if the tumor growth is still showing signs of reduction from pre-treatment values [Band and Kocandrle, 1975]. (2) responses are expected to be rare due to the largely cytostatic nature of the agents, (3) historical benchmarks for PFS have limited utility in small studies in a heterogeneously and heavily pre-treated patient population and also due to the unknown impact of changes implemented as part of the new RECIST 1.1 criteria [Piatek, et al, abstract #2563, ASCO 2011] and current scanning technology and schedules; (4) the effect of patient selection in referral cancer centers raises questions about single arm PFS results given variability of tumor growth rates, and (5) the limited patient population due to mutation specific selection precludes using designs employed in the larger randomized Phase II lung cancer studies in the consortium. These challenges highlight the need for considering novel approaches to evaluating this drug combination in this setting.

   To address these multiple concerns, we will attempt to obtain a tumor growth estimate for each patient's disease on the last erlotinib-based therapy. As patients will "fail" treatment on prior EGFR TKI, we will be usually be able to obtain at least two scans on the prior treatment to estimate the tumor growth rate, which will be estimated using an exponential growth model, providing a straight-forward estimate of the tumor doubling times.

Additional scans will be used if available, and this will provide a unique look at the growth kinetics of lung cancer while being treated with EGFR TKIs. Patients whose progression is not measurable will be excluded from this endpoint, and when progression is based on new sites of disease, the previous tumor growth rate will be considered in the evaluation.

Based on tumor growth rates, we can identify patients where the tumor doubling time has increased by at least 30% from the observed tumor growth rate during the prior TKI treatment, using each patient as their own control. This information will also be considered, along with toxicity and tolerability in both the interim and final analysis.

Patients will come off study after progression, unless, in the opinion of the treating physician, the tumor doubling time continues to be more than 15% longer than the previous growth rate, and it is considered the best option for the patient. [Tumor doubling time in the presence of multiple lesions will be taken as the median tumor doubling time when each tumor is considered independently].

2. Additional secondary endpoints will include the type, severity (by NCI CTCAE), time of onset, duration, and outcome of toxicities, as well as progression-free survival rates and correlative tumor assays. Toxicity will be graded according to the NCI CTCAE version 4.0. Demographic and baseline clinical information will be collected. All radiographic responses will be evaluated by RECIST criteria and will be presented as waterfall plots. Survival and time to treatment failure will be summarized with Kaplan-Meier plots. Subset analysis by number of prior therapies, and prior erlotinib sensitivity will be evaluated.

3. **Analysis of Correlative Endpoints:** Because of the limited sample size inherent to phase II studies, the analysis of secondary endpoints is primarily exploratory. Standard descriptive methods will be used to summarize the baseline levels and the changes from baseline (i.e. after treatment) which will allow us to examine whether observed patterns are consistent with hypothesized patterns. For example, the role of various EGFR mutations and other correlatives (e.g. MET amplification, VEGF and HGF levels) will also be considered. If the combination is not found to have sufficient activity, these patterns may help explain the lack of activity. If sufficient activity is found, then patients who experience an objective response will be compared to those who did not in terms of these correlates. Estimates of variation will also prove useful for future clinical research on this regimen. Formal testing of these comparisons is not planned. All analysis will clearly document the exploratory nature of these studies, although no attempt will be made to adjust for multiple comparisons inherent in correlative studies.

13.4 For phase 2 protocols only: Reporting and Exclusions

13.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with XL184 (cabozantinib) and erlotinib. NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) will be used. Unacceptable toxicity will be defined as any treatment-related (possible or higher attribution) toxicity that results in a >4 week delay in treatment or any toxicity resulting that the patient be taken off treatment. If in first 3 cycles, there are 3 patients with unacceptable toxicities in the first 10 patients, 4 in the first 16, 5 in the first 20, or 20% thereafter, the study will hold for review with the PI, the Data Safety and Monitoring Committee and the NCI regarding treatment modification or study termination.

13.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) will be included in the main analysis outcomes. All patients will be summarized with regard to tumor response, time to progression, and toxicity. Patients in response categories 4-9 will be considered treatment failures (i.e. classified with disease progression for the purpose of calculating response rates and disease control rates). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

14. CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase II trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose

escalation, expansion, as well as decisions to terminate escalation, and

(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCCP teleconference meeting for review and approval.

Oversight

Oversight of the conduct of CCCP trials occurs at several levels:

1. The Data Coordinating Center for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCCP institution; this audit is initiated by CTEP. For all other CCCP trials, the CCCP will contract with Theradex to audit patient records at each CCCP institution.

3. An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 3 voting members (2 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCCP studies, and a statistician) and a non-voting CCCP statistician.

    a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
    b. This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
    c. The DSMC will report to the CCCP leadership.

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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 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. 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.

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

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

The patient _____ is enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib) and erlotinib**. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

XL184 (cabozantinib and erlotinib interact with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

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

XL184 (cabozantinib) and erlotinib interact with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is **CYP3A4**. This enzyme breaks down XL184 (cabozantinib) and erlotinib, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. XL184 (cabozantinib) and erlotinib must be used very carefully with these medicines, or you may need to switch to alternate medications.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers of **CYP3A4**."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a

day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.

- If you drink grapefruit juice or eat grapefruit or Seville oranges: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking XL184 (cabozantinib and erlotinib).

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **XL184 (cabozantinib) and erlotinib**. This clinical trial is sponsored by the NCI. **XL184 (cabozantinib) and erlotnib** interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**XL184 (cabozantinib) and erlotinib** interact with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers or inhibitors of **CYP3A4**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

CTEP-assigned Protocol # 9303
Consortium Protocol PhII-125
Local Protocol # _____

APPENDIX D PATIENT'S MEDICATION DIARY

PATIENT'S MEDICATION DIARY

Today's date _____ **Cycle Number:** _____ **Agents:** XL184 (**Cabozantinib) and Erlotinib**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take XL184 (c**abozantinb) tablets by mouth every day (or every other day)**. You should take the tablets on an empty stomach at least 2 hours before food and 1 hour after a meal. Dose: take _____ 20 mg tablets.
3. You will take **Erlotinib tablets by mouth once a day**. You should take the tablets on an empty stomach at 2 hours before food and 1 hour after a meal. Dose: take _____ x _____ mg tablet(s).
4. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of XL184 (cabozantinib) and Erlotinib tablets when you return for each appointment.

Day	**Date**	**Time of dose**	XL184 (cabozantinib) # of tablets taken **mg**	Erlotinib # of tablets taken **mg**	**Comments**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
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31					

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ 2. Date patient was removed from study_____
3. Patient's planned total daily dose _____
3. Total number of tablets taken this month **XL184 (cabozantinib)**_____ **Erlotinib**_____
4. Physician/Nurse/Data Manager's Signature

APPENDIX E CCCP REGISTRATION PROCEDURES FOR PHASE II TRIALS

1. Registrations for Phase II protocols must be made through the California Cancer Consortium office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).

2. Patients must be registered within 5 days prior to initiation of protocol therapy.

3. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the City of Hope Data Coordinating Center (DCC) at (626) 256-HOPE (4673), ***extension 65928.***

4. Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to study calendar/protocol.

5. Patients must sign an informed consent prior to registration.

6. Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.

7. Complete the Eligibility Checklist.

8. Verify that all required prestudy tests were performed.

9. Email the completed Eligibility Checklist, signed and dated informed consent, pathology report, and relevant laboratory results to the City of Hope Consortium Coordinator for confirmation of eligibility. The email is cccp@coh.org.

10. Call the City of Hope Consortium Coordinator at (626) 256-HOPE (4673), extension 65928 to confirm the email sent. If the Consortium Coordinator is not in the office, have them paged at (626) 423-5365.

11. If the patient qualifies, the City of Hope Consortium Coordinator will call the registering institution to complete the registration/randomization procedure and assign the patient's study ID number.

12. Once a patient has been registered, the Data Coordinating Center will provide a "Confirmation of Registration" to the center registering the patient.

For questions regarding eligibility call City of Hope California Cancer Consortium, Data Coordinating Center
(626) 256-HOPE (4673), extension 65928

APPENDIX F CCCP SPECIMEN SUBMISSION FORM

Please contact the Data Coordinating Center at cccp@coh.org for the CCCP Specimen Submission Form. The form will be emailed to the participating institution when the study has been activated.

APPENDIX G CORRELATIVE STUDIES

Collection, processing and shipment

• Cryovials (1.5 – 2 mL size) must be labeled with the protocol number (**PhII-125**), Consortium patient ID, patient's initials, date of specimen collection, and specimen type.

• Collect ~8 mL whole blood in a purple top (EDTA) tube.

• Immediately invert tube (gently) 8 – 10 times. This reduces the possibility of clot formation.

• Place tube on wet ice or refrigerate until centrifugation.

• Within 2 hours of blood draw, centrifuge sample at **800 x G for 10 minutes**.

• Immediately after centrifuging, transfer **plasma** in **1 mL aliquots to 4 labeled cryovials**.
- Pipette slowly to avoid disturbing the buffy coat layer.
- Leave a small amount of plasma (~ .5 cm) above the buffy coat layer.

• After removing plasma, transfer **buffy coat** to **1** labeled cryovial.
- The buffy layer is the off-white layer between the plasma and the red blood cells.
- Pipette slowly in a circular motion to obtain as many buffy coat cells as possible.
- Contamination of the buffy coat with red blood cells is expected and not a concern. There is no need to further purify the white blood cells with a Ficol separation.

• Snap-freeze cryovials in liquid nitrogen (if available).

• Store cryovials in a -70° C freezer until shipped.

Shipping Instructions
Prior to shipping, the Specimen Submission Form (please email cccp@coh.org for a copy of the form) should be faxed to the Statistical Center at the City of Hope AND the Mack lab (916-734-2361).

The frozen specimens (along with completed Specimen Submission Forms) should be shipped **on dry ice** by overnight courier **Monday through Wednesday** to:
Philip C. Mack, Ph.D.
Division of Hematology/Oncology
University of California, Davis Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817

Contact:
Leslie J. Snyder or Philip C. Mack
Phone: 916/734-3734
E-mail: Leslie.Snyder@ucdmc.ucdavis.edu

The Federal Guidelines for Shipment are as follows:

6. The specimen must be wrapped in an adsorbent material;

7. The specimen must be placed in an AIRTIGHT container (resealable bag);

8. Pack the resealable bag and specimen in a Styrofoam shipping container along with enough dry ice to last for 2 days;

9. Pack the Styrofoam shipping container in a cardboard box;

10. The cardboard box must be labeled with a Hazardous Materials label for the Dry Ice.

APPENDIX H GUIDELINES FOR TISSUE BIOPSIES

Definitions

- Invasive biopsies: accessing thorax, liver, or soft tissue or deep nodes within the abdomen

- Minimally invasive biopsies(and thoracentesis/paracentesis): superficial nodes, cutaneous or superficial lesions, bone biopsies, abdominal ascites or pleural effusions (when collection occurs for patient management)

Collection Windows

- Invasive biopsies: All invasive biopsies should be completed 28 days prior to first dose of cabozantinib. No invasive biopsies should be performed while on cabozantinib treatment. Subsequent invasive biopsy procedures should not be performed within 21 days after last dose of cabozantinib if possible due to the half life of the drug.

- Minimally invasive biopsies(and thoracentesis/paracentesis): Minimally invasive biopsies are allowed at any time prior to first dose and while the subject is on cabozantinib treatment, providing that attention is given to potential effects of cabozantinib on wound healing, fistula formation or perforations. No tumors continguous with the esophagus or trachea should be accessed while on cabozantinib treatment"