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Brief Title: Cabozantinib in Advanced Pancreatic Neuroendocrine and Carcinoid Tumors

Full Title: **An Open-Label, Phase II Study of Cabozantinib (XL184) in Advanced Pancreatic Neuroendocrine and Carcinoid Tumors**

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SCHEMA

Patients with advanced neuroendocrine tumors (PNET or carcinoid) with documented radiographic progression.

1. OBJECTIVES

1.1 Study Design

The current study is an open-label, Phase II study of patients with advanced carcinoid or pancreatic neuroendocrine tumors with progressive disease. A total of 70 patients will be enrolled with advanced neuroendocrine tumors: 35 patients with advanced carcinoid tumors and 35 patients with pancreatic neuroendocrine tumors. The estimated time for accrual of the patients is 18-24 months. This study will include a Pre-Treatment Period (screening and baseline evaluations), a Treatment Period (consisting of 4-week cycles of cabozantinib administered daily orally at a dose of 60 mg, and a Post-Treatment Period (consisting of a post-treatment visit 30 days [+7] after the last dose of study treatment, with follow-up information obtained every 12 weeks post last dose thereafter until final survival status is determined). Tumor assessments will be performed after the second, fourth, and sixth cycles, then every third cycle (± 5 days) following randomization until documented disease progression per RECIST by the investigator or end of treatment at the physician's discretion.

1.2 Primary Objectives/Endpoints

1.2.1 Evaluate objective response rate of cabozantinib.

1.3 Secondary Objectives/Endpoints

1.31 Determine progression-free and overall survival in patients receiving cabozantinib.
1.32 Assess safety and tolerability of cabozantinib.
1.33 Define molecular and imaging correlates of response, pending funding availability including dynamic/ perfusion CT, and circulating biomarkers.

2 BACKGROUND

2.1 Investigational Agent

Cabozantinib (XL184) is a new chemical entity that exhibits potent inhibitory activity against several receptor tyrosine kinases known to influence tumor growth, metastasis, and angiogenesis. The primary targets of cabozantinib are MET and VEGFR2/KDR, with IC50 (concentration associated with 50% inhibition) values of 1.8 and 0.035 nM, respectively. The in vitro target inhibition profile of cabozantinib is shown in Table 1-1.

Table 2-1
Inhibition of Key Protein Kinases by Cabozantinib in Biochemical, Enzymatic Assays

Kinase	IC_{50} ± SEM (nM)
MET	1.8 ± 0.2
VEGFR2/KDR	0.035 ± 0.007
RET	9.8 ± 2.3
KIT	4.6 ± 0.5
VEGFR1/FLT-1	12.2 ± 0.7
VEGFR3/FLT-4	6.0 ± 0.6
AXL	7
TIE-2	14.3 ± 2.8
FLT-3	14.4 ± 0.8

IC_{50}, concentration required for 50% target inhibition; VEGFR2, vascular endothelial growth factor receptor 2.

Data from pharmacodynamic experiments have shown that cabozantinib inhibits MET and VEGFR2 in vivo. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts in nude mice and blockade of VEGFR2 phosphorylation in mouse lung tissue. The duration of action for cabozantinib was sustained, with > 50% inhibition observed 10-24 hours post-dose at a dose level of 100 mg/kg for all targets studied.

Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 hours after administration. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC (thyroid), breast cancer, lung carcinoma, and GB (brain) (Table 1-2).

Table 1-2: Cabozantinib ED_{50} Values in Tumor Efficacy Models

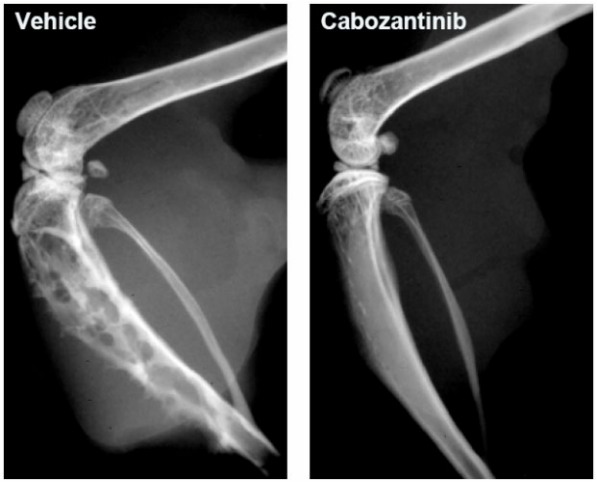
Tumor Cell Line	Species	Tissue of Origin	ED_{50} (mg/kg/day)	Treatment Duration
C6	Rat	Brain	< 1	qd × 12
MDA-MB-231	Human	Breast	2	qd × 14
H441	Human	Lung	3	qd × 14
TT	Human	Thyroid	11	qd × 21

ED_{50}, dose associated with 50% tumor growth inhibition; qd, once daily.

Activity of Cabozantinib in the Transgenic RIP-Tag2 Model System
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 (Pàez-Ribes et al. 2009). Treatment with cabozantinib for 3 weeks, from age 14 to 17 weeks, significantly blocked liver metastasis in the RIP-Tag2 model compared with anti-VEGF treatment or vehicle alone. The number of liver metastases was 5-fold greater in anti-VEGF antibody-treated animals compared with vehicle-treated animals, and no liver metastases were detected in cabozantinib-treated animals. In addition, treatment with cabozantinib from age 14 to 20 weeks improved survival. Median survival was 14.7 weeks for vehicle-treated animals (n = 12) and 16.4 weeks for anti-VEGF antibody-treated animals (n = 7; $P < 0.05$ vs. vehicle), and all cabozantinib-treated animals survived for the full 20 weeks of observation (n = 6; $P < 0.05$ vs. vehicle and anti-VEGF antibody).

Activity of Cabozantinib in a Preclinical Bone Metastasis Model
The human prostate cancer model ARCaP-M, which expresses both MET and the VEGF co-receptor NP-1 (Zhang et al 2010), was used in a prostate tumor xenograft study in bone. ARCaP-M cells were injected into the tibiae of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive cabozantinib or vehicle qd for 7 weeks of treatment. As shown in the representative x-ray images (Figure 1-1), tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from cabozantinib-treated animals appeared mostly normal. Thus, cabozantinib treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Figure 1-1: ARCaP-M Prostate Tumor Model: Vehicle vs. Cabozantinib (X-Ray Images)



Cabozantinib Nonclinical Toxicology

Cabozantinib nonclinical toxicology has been characterized in single- and repeat-dose studies in multiple species. In nonclinical toxicology studies of cabozantinib in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues, and secondary changes were observed in bone and pancreas. Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, and decreased fertility in male and female rats. Details can be found in the Investigator Brochure.

2.1.1 Clinical Experience and Activity

Cabozantinib has demonstrated broad clinical activity in multiple tumor types, including thyroid, breast, ovarian, prostate, and lung cancers, melanoma, glioblastoma (GB), hepatocellular carcinoma (HCC), and renal cell carcinoma (RCC). Observations of clinical activity have included shrinkage of soft tissue tumor lesions including visceral metastases, effects on metastatic lesions on bone scan (partial or complete bone scan resolution), reduction in serum markers of bone resorption and formation, increases in hemoglobin, and improvements in bone pain and reductions in narcotic use in subjects with bone metastases. In the Phase 1 Study XL184-001, with an enriched medullary thyroid cancer (MTC) population, confirmed partial response (cPR) (with duration up to 48+ months) was reported in 29% of MTC subjects, and stable disease (SD) of at least 6 months was reported in 41% of MTC subjects. In the Phase 2 randomized discontinuation trial, Study XL184-203, disease control rates (DCR; defined as SD or confirmed response) at Week 12 ranged from 40-73% in the six cohorts for which cabozantinib had the greatest activity: non-small cell lung cancer (NSCLC), 40%; breast cancer, 45%; melanoma, 47%; ovarian cancer, 55%; castration-resistant prostate cancer (CRPC), 68%; and HCC, 73%. Please refer to the current version of the Investigator's Brochure for updated information regarding the clinical experience of cabozantinib.

2.1.2 Clinical Safety Profile

As of 04 May 2011, 1333 subjects have been enrolled in clinical studies with cabozantinib, for which serious adverse event (SAE) data are available (1003 subjects in open-label clinical studies with cabozantinib and 330 subjects in the blinded Study XL184-301, randomized 2:1 for cabozantinib versus placebo). As of 01 March 2011, adverse event (AE) data are available for 913 subjects who have been dosed with cabozantinib in open-label clinical studies (806 subjects in single-agent cabozantinib studies and 107 subjects in combination studies of cabozantinib with erlotinib, rosiglitazone, or temozolomide [TMZ] ± radiation). These subjects have been treated with cabozantinib at salt weight doses ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule and from 25 mg (19.7 mg freebase equivalent weight) to 265 mg (209 mg freebase equivalent weight) on a fixed daily dosing schedule. Refer to the current version of the Investigator's Brochure for detailed information regarding the safety profile of cabozantinib across all studies.

2.1.2.1 Adverse Events

The most commonly reported SAEs that were assessed as related to study treatment with cabozantinib (as a single-agent or part of a combination treatment) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome. Ten percent of subjects were reported to have discontinued study treatment due to an AE, most frequently fatigue. There have been 15 deaths assessed as 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). Details for these and 13 additional deaths assessed as not related to study treatment are provided in this Investigator's Brochure.

2.1.2.2 Serious Adverse Events

As of 04 May 2011, of the 1003 subjects enrolled in open-label clinical trials with cabozantinib (either as a single-agent or in combination with other therapies), 473 subjects (47%) experienced one or more SAEs, and 199 subjects experienced one or more SAE that was assessed as related to treatment with cabozantinib. The majority of SAEs were attributed to the underlying cancer. The most commonly reported SAEs that were assessed as related to study treatment with cabozantinib (as a single-agent or part of a combination treatment) were PE, diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome. In the blinded study of cabozantinib versus placebo (Study XL184-301) in subjects with MTC SAEs of one Grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one Grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three of acquired tracheo-esophageal fistula (two Grade 3, one Grade 5) were reported.

Deaths

As of 04 May 2011, across all open-label studies (single-agent cabozantinib and cabozantinib in combination with other therapies), there have been 15 deaths assessed as 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).

2.1.3 Clinical Pharmacokinetics

Pharmacokinetic analysis showed dose proportional increases in maximum plasma concentration (Cmax) and area under the plasma concentration time curve (AUC) both for the powder-in-bottle (PIB) formulation (dose range: 0.08 to 11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg). Terminal-phase half-life (t1/2, z) values were 59.1 to 136 hours. More detailed information regarding cabozantinib PK from all studies and product metabolism in humans may be found in the Investigator's Brochure.

Pharmacokinetics and Product Metabolism in Humans

2.1.3.1 Phase 1: Study XL184-001
In Study XL184-001, a preliminary PK analysis has been performed for 74 subjects. The cutoff date for the data used for this PK analysis was 02 September 2008. In an analysis of PK data on subjects (Cohorts 1-9) receiving cabozantinib as an oral suspension at 0.08 to 11.52 mg/kg on the Intermittent 5&9 schedule, values for C_{max} and AUC from 0 hours to the last sampling time point ($AUC_{0\text{-}last}$) increased generally dose-proportionally. The $t_{1/2,\ z}$ values were long (range: 59.1 to 136 hours).

Data from Cohorts 10--13 (175 mg PIB qd; 265 mg PIB qd; 175 mg capsule formulation qd; 250 mg capsule formulation qd) and the eMTD Cohort (175 mg capsule formulation qd) show that drug accumulation (based on C_{max} and $AUC_{0\text{-}24}$ values) at steady-state after qd dosing is approximately 4- to 6-fold. In addition, exposure values from PIB (Cohort 10) or the capsule formulation (Cohorts 12 and eMTD Cohort) are compared in Table 5 2. The data are limited by a small sample size but show that cabozantinib exposure (AUC) values from capsule-formulation cohorts are about 2-fold greater than those observed in the respective PIB Cohort.

Table 2.1.3.1: Comparison of Exposure from PIB (Cohort 10) or Capsule Formulation (Cohorts 12 and eMTD Cohort)	**D19 C_{max} (ng/mL)**	**D19 AUC (ng•h/mL)**
Cohort 10 175 mg qd PIB, n = 3	1410	21200
Cohort 12 and eMTD Cohort 175 mg qd capsule formulation, n = 19	2310	41600

AUC, area under the plasma drug concentration time curve; C_{max}, maximum plasma concentration; eMTD, expanded maximum tolerated dose; PIB, powder-in-bottle (formulation); qd, once daily.

2.1.3.2 Phase 1: Study XL184-002
As of 15 March 2010, PK data were available from three subjects enrolled in the first cohort of Arm 1a (cabozantinib 75 mg qd + TMZ 75 mg/m^2 qd + radiotherapy). Intensive PK sampling was conducted during the concurrent treatment phase on Days 1 and 29. The observed Day 1 mean exposure values for TMZ were close to published reference values at 75 mg/m^2 (ie, Day 1 AUC: 10.3 ± 0.913 µg•hour/mL vs 12.1 ± 1.1 µg•hour/mL, from Ostermann et al. 2004). Similarly, mean steady-state exposure values (AUC) for cabozantinib (18.0 ± 0.818 µg•hour/mL) were comparable to those extrapolated from Study XL184-201 (17.5 µg•hour/mL, predicted from observed values at 125 mg), a Phase 2 trial in which subjects with GB are receiving cabozantinib monotherapy. Sparse PK samples were also available from three subjects in Arm 2a (cabozantinib 75 mg qd + TMZ 200 mg/m2/day on Days 1-5 of every 28-day cycle). Results show that the mean steady-state concentration values for cabozantinib at 4 hours post-cabozantinib dose (801 ± 182 ng/mL) were very close to those extrapolated from Study XL184-201 (810 ng/mL, estimated from observed values at 125 mg). Overall, the preliminary data show no apparent metabolic (exposure) drug-drug interaction between cabozantinib and TMZ.

2.1.3.3 Phase 1: Study CA205-001

Pharmacokinetics of cabozantinib were evaluated for three subjects after a single dose on Day 1 and for two subjects at steady-state on Day 19. Exposure values for C_{max} and AUC_{0-24} were 4- to 5-fold higher than that observed for Day 1, which was consistent with the observation in Study XL184-001 of the magnitude of cabozantinib accumulation after repeated qd dosing.

2.1.3.4 Phase 1: Study XL184-008

The XL184-008 study is designed as a two-treatment two-period single-sequence crossover study to test cabozantinib for inhibition of the CYP2C8 pathway. Rosiglitazone, a known CYP2C8 substrate, is administered on Day 1, and PK samples are obtained over 24 hours. Starting on Day 2, cabozantinib is administered qd at a dose level of ≥ 125 mg/day (salt weight) for 21 days to achieve steady-state levels of cabozantinib. Rosiglitazone is then administered again on Day 22, 1 hour after the twenty-first dose of cabozantinib, and PK sampling is repeated over a 24-hour period. As of 17 May 2011, preliminary PK data were available from 20 subjects, 16 of whom were evaluable on both Day 1 and Day 22. Based on the data for these 16 subjects, the geometric mean Day 22:Day 1 ratio of rosiglitazone AUC_{0-24} was 1.00 (90% confidence interval [CI]: 0.921.09), and the corresponding ratio for C_{max} was 0.92 (90%CI: 0.78-1.09). Furthermore, both C_{max} and AUC_{0-24} were similar on Day 1 and Day 22 for desmethyl-rosiglitazone, a metabolite of rosiglitazone generated via a CYP2C8 metabolic pathway. Based on these preliminary data, there was no evidence for marked inhibition of rosiglitazone metabolism, suggesting that cabozantinib does not inhibit the CYP2C8 pathway at clinically relevant concentrations.

2.1.3.5 Phase 1b/2: Study XL184-202

Table 2.3.1.5: Exposure (AUC) Values in Subjects with NSCLC Following Administration of Erlotinib or Cabozantinib Cohort	**Cabozantinib Dose (mg)**	**Erlotinib Dose (mg)**	**Erlotinib AUC, without Cabozantinib (µg•h/mL)**	**Erlotinib AUC, with Cabozantinib (µg•h/mL)**	**Cabozantinib AUC (µg•h/mL)**
1	75	150	83.9 (49.8%, n = 3)	36.6 (n = 1)	28.6 (n = 1)
2A	75	100	23.6 (27.1%, n = 12)	27.0 (28.8%, n = 6)	18.0 (27.6%, n = 6)
2B	50	150	38.0 (35.5%, n = 16)	36.0 (36.4%, n = 12)	13.3 (37.7%, n = 12)
3A	125	100	26.9 (52.8%, n = 12)	19.9 (39.9%, n = 7)	18.3 (29.9%, n = 8)
4A	125	50	12.3 (n = 2)	17.1 (45.5%, n = 3)	21.6 (45.5%, n = 3)

AUC, area under the plasma drug concentration time curve; CV, coefficient of variation.
Note: AUC values are presented as mean (%CV).

As of 17 February 2010, PK data available for 5 cohorts (n = 1–16 subjects/cohort) showed that exposures to cabozantinib at doses of 50-125 mg or erlotinib at doses of 50-150 mg were not apparently affected by co-administration of both drugs. Exposure (AUC) values of cabozantinib at doses of 50-150 mg were close to the levels estimated from PK data of Study XL184-001 in which cabozantinib was administered as a single agent (dose range: 0.08 to 11.52 mg/kg). In addition, AUC values for erlotinib at doses of 50-150 mg before or after co-administration of cabozantinib are not markedly different (Table 2.1.3.5).

Table 2.1.3.5: Cabozantinib Concentration Values in Subjects with Glioblastoma **Concentration Values**	**125 mg qd**	**175 mg qd**
C1D15 pre-dose	1260 ± 566 ng/mL (n = 109)	1680 ± 750 ng/mL (n = 29)
C1D15 4 hours post-dose	1370 ± 601 ng/mL (n = 100)	2020 ± 1060 ng/mL (n = 27)
d, once daily.		

In addition, intensive PK samples were taken from 15 subjects receiving a capsule dose of 125 mg qd. Consistent with an approximately 30% lower dose, steady state mean values of C_{max} and AUC_{0-24} for 11 of these subjects were approximately 40% lower compared to subjects treated at 175 mg qd in Study XL184-001 (C_{max}: 1390 ng/mL [125 mg] vs 2310 ng/mL [175 mg]; AUC: 26,500 ng•h/mL [125 mg] vs 41600 ng•h/mL [175 mg]). Consistent with the observations for sparse sampling at pre-dose and post-dose, an approximately dose-proportional increase in C_{max} and AUC at steady-state was observed between 125 and 175 mg; a 1.6-fold increase in exposure was observed as the dose increased by 1.4-fold.

2.1.3.6 Phase 2: Study XL184-203

As of 12 June 2011, sparse plasma drug concentration data from the Lead-In Stage of the RDT study, XL184-203, were available across all nine tumor type cohorts (n = 149 subjects). Steady-state trough concentrations on Day 42 (ie, at the end of Week 6) were summarized after excluding subjects with documented prior dose holds or dose modifications (Table 2.1.3.6). Based on this preliminary analysis, no clear evidence was found to suggest that any one tumor type had markedly different steady-state trough concentrations or variability in steady-state trough concentrations compared with the other tumor types studied.

Table 2.1.3.6

Tumor-Type Cohort	Statistic[a]	Plasma Cabozantinib Pre-Dose Concentration at End of Week 6 (ng/mL)
Prostate[b]	N	46
	Mean	1121
	SD	509
	CV%	45.4
Breast	N	7
	Mean	1140
	SD	796
	CV%	69.8
Gastric/GEJ[b]	N	8
	Mean	1132
	SD	478
	CV%	42.2
Hepatocellular	N	5
	Mean	1041
	SD	335
	CV%	32.2
Melanoma	N	26
	Mean	1008
	SD	433
	CV%	43.0
NSCLC	N	15
	Mean	1292
	SD	739
	CV%	57.2
Ovarian	N	30
	Mean	1307
	SD	653
	CV%	49.9
Pancreatic	N	6
	Mean	814
	SD	543
	CV%	66.8
SCLC	N	6
	Mean	1115
	SD	591
	CV%	53.0

CV, coefficient of variation; GEJ, gastroesophageal junction; NSCLC, non-small cell lung cancer; PK, pharmacokinetic; SD, standard deviation; SCLC, small cell lung cancer.

[a] Subjects with prior dose holds or reductions prior to PK sampling at the end of Week 6 were excluded from the summary statistics.

[b] One subject in the Gastric/GEJ Cohort and two subjects in the Prostate Cancer Cohort were excluded from the summary statistics due to very low plasma cabozantinib concentrations (ie, < 300 ng/mL).

The starting dose of single agent cabozantinib in this study will be 60 mg daily (free base weight). While the MTD of single-agent cabozantinib from the Phase 1 study (XL184-001) was 175 mg, in both the XL184-201 *and XL184-203* studies, anti-tumor activity has also been observed at starting doses of cabozantinib lower than 175 mg.

Based on in vivo target modulation studies, cabozantinib exhibited IC50 values (concentration required for 50% inhibition) between 2 and 7.4 μM for MET, VEGFR2, and RET (Table 2.1.4).

Table 2.1.4

Target	Model	Dose Response: Maximum Inhibition (%)	Dose Response: Estimated ED_{50} (mg/kg)	Dose Response: Estimated IC_{50} (μM)	Duration of Action: Dose (mg/kg)	Duration of Action: Maximum Inhibition (%)	Duration of Action: Sustained Inhibition > 50% (hours)
MET	Liver (+HGF)	97	5	2	100	99	10
	H441	96	9	7	100	92	10
VEGFR2	Lung (+VEGF)	98	26	2	100	99	10
TIE-2	Lung (basal)	84	86	24	100	58	4
RET	TT	89	11	8	100	79	< 24

MET, hepatocyte growth factor receptor protein; TIE-2, receptor for angiopoietin-1 and -2; VEGFR2, vascular endothelial growth factor receptor 2

ED_{50}, dose associated with 50% inhibition (of receptor phosphorylation); HGF, hepatocyte growth factor; IC_{50}, concentration associated with 50% inhibition (of receptor phosphorylation); TT, medullary thyroid carcinoma cell line; VEGF, vascular endothelial growth factor.

2.1.4 Clinical Pharmacodynamics

Data from pharmacodynamic experiments show that, in vivo, cabozantinib inhibits key RTKs that promote tumor cell proliferation and/or angiogenesis (MET, VEGFR2, TIE-2, and RET). This provides support for the hypothesis that the efficacy of cabozantinib against multiple tumor types potentially results from inhibition of both tumor cell division and angiogenic responses. In general, there was a good correlation between increases in plasma drug concentrations and increased inhibition of receptor phosphorylation at the doses tested. Results from dose-response experiments in mice indicated that the ED_{50} of targets was achieved at well tolerated doses of cabozantinib at plasma exposure comparable to exposure observed in clinical trials.

2.1.4.1 Pharmacodynamic Findings in Humans: Phase 1: Study XL184-001

2.1.4.1.1 Plasma Sample Collection for Pharmacodynamic Analyses

Plasma samples were analyzed for several biomarkers of response to anti-angiogenic agents, including levels of VEGF-A, soluble VEGFR2 (sVEGFR2), and placental growth factor (PlGF). Clinical studies have shown increases in VEGF-A and PlGF and decreases in sVEGFR2 in response to treatment with anti-angiogenic agents other than cabozantinib (Motzer et al. 2006).

Changes in pharmacodynamic markers consistent with anti-angiogenesis activity were observed in Cohorts 6 through 12 and the eMTD Cohort with plasma samples taken on Day 1 pre-dose and Day 29. While small cohort sizes presented a challenge for statistical analysis of pharmacodynamic marker changes the combined data of Cohorts 12 and the eMTD Cohort (ie, subjects enrolled at the MTD) demonstrated that changes in PlGF (↑), VEGF-A (↑), EPO (↑), and sVEGFR2 (↓) reached statistical significance. Soluble MET as a potential biomarker of MET inhibition was increased upon cabozantinib treatment and changes reached statistical significance. Changes in these pharmacodynamic biomarkers were also observed in earlier cohorts and reached statistical significance for some time points and/or some cohorts. Analysis of potential correlations between maximal tumor shrinkage (unaudited data) and baseline levels

of plasma biomarkers revealed that Ang2, EPO, and OPN significantly ($P < 0.05$) correlate with tumor response across multiple tumor types (MTC: n = 29, melanoma: n = 4, colorectal carcinoma: n = 3, other n = 10 [with n = 1 per tumor type]) and thus might represent potential prognostic biomarkers. Predictive biomarkers correlating with tumor shrinkage could not be identified.

Similar data showing modulation of plasma markers of anti-angiogenesis therapy by cabozantinib treatment have been obtained from several other clinical studies, including XL184-201 (see Section 2.1.4.3) and XL184 202 (not shown).

2.1.4.1.2 Determination of Mutational RET Status in Tumor Tissue and/or Whole Blood Samples
Germline and somatic RET genotyping was performed on DNA isolated from whole blood (n = 29) and tumor (n = 27), respectively, for the subjects with MTC. Activating RET mutations were detected in 25/31 (81%) of MTC tumors. Of note, the tumor of one subject with MTC with rapid clinical progression demonstrated the P-loop, BRAF activating mutation G469A, the absence of a detectable RET mutation, and a 2.2-fold amplification of the MET gene. Of the four remaining tumors without detectable RET mutations, one was found to have a 1.7-fold amplification in MET. The genotyping data suggest the absence of a correlation between RET mutations and either clinical response or time on study.

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

2.1.4.2 Pharmacodynamic Findings in Humans: Phase 1b/2: Study XL184-202
2.1.4.2.1 Molecular Analysis
Molecular analyses included the determination of EGFR mutations and MET gene copy number status. Based on preliminary data, clinical activity of cabozantinib in combination with erlotinib was observed in a largely erlotinib-pretreated population, which included patients with the EGFR T790M mutation and with and without MET amplification (Wakelee et al. 2010).

2.1.4.3 Phase 2: Study XL184-201
2.1.4.3.1 Plasma Sample Collection for Pharmacodynamic Analyses
Plasma samples were analyzed for several biomarkers of response to anti-angiogenic agents, including levels of VEGF-A, sVEGFR2, and PlGF. Changes in pharmacodynamic markers consistent with cabozantinib on-target effects were observed after cabozantinib administration in 40 subjects treated with a starting dose of 175 mg. Changes in PlGF (↑), VEGF-A (↑), sVEGFR2 (↓), and sKIT(↓) reached statistical significance at multiple time points, particularly Days 15 and 29, on which the largest amount of data was available. Soluble MET as a potential biomarker of MET inhibition was modulated (↑) upon cabozantinib treatment and changes reached statistical

significance as well, on Day 15 and Day 57 (Cycle 3 Day 1), though changes were less robust than those for the analytes listed above. Baseline plasma levels of VEGF-A and PlGF were markedly higher in subjects that had received prior treatment with agents that directly target VEGF (ie, bevacizumab [n = 6] and VEGF-Trap [n = 1]) compared to subjects who either had no prior anti-angiogenic treatment or had treatment with anti-angiogenic agents that do not target VEGF directly (14-fold higher for VEGF-A; 2-fold higher for PlGF; both $P < 0.001$). Preliminary analysis of potential correlations between clinical outcome and baseline levels or changes during treatment of the plasma proteins did not reveal significant correlations other than a trend observed towards lower baseline bFGF in subjects with PR compared to subjects with PD in fewer than 8 weeks ($P = 0.05$).

Results from a similar analysis of plasma samples obtained from subjects treated with a starting dose of 125 mg showed statistically significant modulation of plasma biomarkers VEGF-A, PlGF, and sVEGFR2, as well as modulation of sKIT and sMET. Mean fold-changes from baseline at Day 15 of treatment (pre-dose) were as follows (N = 29): VEGF-A: 1.8-fold increase; PlGF: 2.7-fold increase; sVEGFR2: 17% decrease (ratio of 0.83); sKIT: 11% decrease (ratio of 0.89). As in the 175-mg cohort, baseline plasma levels of VEGF-A and PlGF in the 125-mg group were markedly higher in subjects that had received prior treatment with bevacizumab [n = 8] compared to subjects who either had no prior anti-angiogenic treatment or had treatment with anti-angiogenic agents that do not target VEGF directly [n = 25] (5.7-fold higher for VEGF-A; 1.9-fold higher for PlGF; both $P < 0.001$).

2.1.4.4 Phase 2: Study XL184-203

2.1.4.4.1 Analysis of Pharmacodynamic Plasma Samples

Plasma analyses thus far have focused on the crosslinked C-telopeptide of type I collagen (CTx), a marker of osteoclast activity and bone resorption. Levels of CTx were reduced in the majority of subjects including those with CRPC for whom at least one baseline and a Week 6 or Week 12 plasma sample could be tested. The effects of cabozantinib on decreasing plasma CTx levels appear to be independent of prior or concomitant bisphosphonate treatment or presence of bone metastases (Gordon et al. 2011, Hussain et al. 2011). In addition, total ALP (t-ALP) was routinely measured in serum in these subjects. While t-ALP is also generated in the liver, in men with CRPC with elevated levels, it correlates well with levels of bone-specific ALP, a marker of osteoblast activity and bone formation. Consistent with effects of cabozantinib on osteoblast activity, the majority of CRPC subjects with bone metastases and elevated t-ALP levels at baseline showed reductions in t-ALP. These effects were independent of prior or concomitant bisphosphonate treatment (Hussain et al. 2011).

2.1.4.4.2 Genotyping of Archival Tumor Tissue

Thus far, select genotyping analyses have been conducted on archival tumor tissue and clinical sites have shared their own results when available. Based on the preliminary analysis of 48 melanoma subjects with both tumor response and BRAF mutation data, clinical activity of cabozantinib appears to be independent of BRAF mutation status (Gordon et al. 2011). Clinical activity of cabozantinib also appears to be independent of EGFR and KRAS mutation status in NSCLC subjects based on the preliminary data (Gordon et al. 2011). However, only 4 of 23 NSCLC subjects with available EGFR genotyping data and only 3 of 23 NSCLC subjects with available KRAS genotyping data were positive for a mutation. In the limited samples tested from

the NSCLC Cohort, no MET mutations were detected, and MET amplification status has not been analyzed.

2.1.4.5 Phase 3: Study XL184-301

2.1.4.5.1 Pharmacodynamic Sample Collection and Analysis Plan

Archival tumor samples to determine the RET mutational status in tumors and a whole blood sample to determine the hereditary RET status are being collected from every subject. Plasma samples taken at baseline and intermittently while on treatment are being collected to evaluate changes in plasma markers of anti-angiogenesis therapy. Data analysis is not yet complete. Refer to the current version of the Investigator's Brochure for information regarding the clinical pharmacodynamics of cabozantinib.

2.1.5 Clinical Activity

Preliminary clinical activity data are available for Studies XL184-001, XL184-201, XL184-202, and XL184-203.

XL184-001

Study XL184-001 was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, including 37 subjects with MTC (35 with measurable disease), were enrolled in the XL184-001 study. Of the 85 subjects, 18 subjects experienced a tumor shrinkage of ≥ 30%, including 17 (49%) of 35 subjects with MTC with measurable disease. In the response evaluable subset of subjects with MTC, 10 (29%) of 35 subjects had confirmed partial responses (cPRs). In addition, 15 subjects with MTC had stable disease (SD) for at least 6 months.

XL184-201

Study XL184-201 was designed to evaluate the safety and tolerability and antitumor activity of cabozantinib in subjects with progressive or recurrent GB. Clinical efficacy data are summarized in Table 2.1.5 for 46 subjects who received cabozantinib at a starting dose of 175 mg (Group A) and 59 subjects who received cabozantinib at a starting dose of 125 mg qd (Group B). In both of these cohorts, radiographic response was evaluated by an IRF review of MRI scans per modified Macdonald criteria (Macdonald et al. 1990). An additional cohort with a starting dose of 125 mg qd (Group C) was also enrolled, but clinical efficacy data have not yet been analyzed.

Table 2.1.5: Response Rate and Progression-Free Survival in XL184-201 (N = 105)

	Prior Anti-Angiogenic Treatment			
	Naïve		Pretreated	
Group	A (n = 34)	B (n = 37)	A (n = 12)	B (n = 22)
Dose	175 mg	125 mg	175 mg	125 mg
ORR, n (%)[a]	7 (21)	11 (30)	1 (8)[b]	0
Median duration of response, months (range)[a]	2.9 (1.9-12.8)	5.1 (0.9+ - 6.7+)	NE	NE
Median progression-free survival, weeks[c]	15.9	16.0	14.3	7.9
Progression-free survival at 6 months, %[c]	10	25	38	0

IRF, independent radiology facility; NE, not estimable; ORR, objective response rate.
[a] Per IRF
[b] Duration of response = 12.3 months (subject previously treated with vandetanib)
[c] Per investigator

XL184-202

In Study XL184-202, sixty-four subjects were enrolled in the Phase 1 dose-escalation portion of the study examining the combination of cabozantinib and erlotinib in NSCLC subjects. All but two subjects had been previously treated with and progressed on erlotinib therapy. Nine subjects (14%) had a ≥ 30% decrease in the sum of tumor measurements compared with baseline measurements. A cPR was observed in 5 subjects (8%). In addition, 24 subjects (37%) had SD/PR ≥ 4 months (range, 4.6-23+ months).

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 PD receive single-agent cabozantinib or cabozantinib in combination with erlotinib. Additional details about the design of Study XL184-202 are presented in Section 5.1.5 of the Investigator's Brochure v7. Two subjects (7%) had a ≥ 30% decrease in the sum of tumor measurements compared with baseline measurements (one subject who received treatment with single-agent cabozantinib and one subject who received treatment with cabozantinib in combination with erlotinib). A cPR was observed in the subject who was treated with single-agent cabozantinib.

XL184-203

Study XL184-203 is an ongoing Phase 2 randomized discontinuation study of cabozantinib in subjects with advanced solid tumors, a total of 531 subjects have been enrolled. An analysis of data from the Lead-In Stage for 490 subjects showed clinical activity in multiple tumor types including regression of soft-tissue tumor disease, bone scan resolution in subjects with bone metastasis, and other signs of clinical benefit (Gordon et al. 2011; Hussain et al. 2011; Bukanovich et al 2011). Randomization was suspended in the CRPC and ovarian cancer cohorts based on observed high rates of clinical activity, and randomized subjects were unblinded. Non-randomized expansion (NRE) cohorts have been initiated for these tumor types.

CRPC Cohort (N = 171)

The majority (91%) of enrolled subjects had ≥ 2 disease sites; 37% had evidence of disease in liver or lung, and 87% had metastasis to bone. Forty-three percent of subjects were pretreated with docetaxel, 9% with abiraterone or MDV3100, and 22% with other cytotoxic and/or experimental therapies. Seven subjects achieved a cPR at Week 12, and three additional subjects achieved PR after the 12-week Lead-In Stage. The overall DCR at Week 12 was 68%. Regression of measurable soft-tissue disease was observed in 74% of subjects with at least one post-baseline tumor assessment. Changes in PSA appeared to be independent of radiographic changes.

In 108 CRPC subjects evaluable for post-baseline bone scan changes, best assessments of bone scan were partial or complete resolution in 82 subjects (76%), stable disease in 23 subjects (21%), and PD in three subjects (3%). Based on a retrospective survey completed by investigators, the majority of the subjects reported reduced bone pain and reduced reliance upon narcotic pain medication. There were 83 subjects with bone metastases and bone pain at baseline who had at least one post-baseline assessment of pain status. Of these, 56 subjects (68%) had pain improvement at either Week 6 or 12. There were 71 subjects who required narcotic analgesic medication at baseline for control of bone pain. Among the 67 of these subjects who were evaluable for post-baseline pain improvement, 47 (70%) had pain improvement at Week 6 or Week 12, and among the 55 subjects who were evaluable for post-baseline changes in consumption of narcotics, 31 (56%) were able to decrease or discontinue narcotic medication.

A positive correlation between bone scan resolution and improvement in clinical symptoms of disease was observed. Subjects with bone scan resolution (either complete or partial) were more likely to be free of disease progression at 6 months (61% vs. 35%), experience pain relief (83% vs. 43%), reduce or eliminate their need for narcotic analgesics (68% vs. 33%), achieve tumor regression (78% vs. 58%), and experience substantial declines in markers of bone turnover (60% vs. 43%), as compared to those who did not achieve bone scan resolution (stable or progressing bone scan).

Reductions of t-ALP and CTx were observed. Of 28 subjects with bone metastases who had t-ALP levels at least 2 × ULN, and at least 12 weeks of follow-up, the majority had decreases in t-ALP. In addition, of 118 subjects with bone metastases and plasma CTx data, the majority also showed a decrease in CTx at Week 6 or Week 12. Reductions in either CTx or t-ALP occurred regardless of prior bisphosphonate treatment. The investigator-assessed median PFS of the Randomized Stage, from Week 12 onward, was 6 weeks (95% CI: 5–12 weeks) for the placebo group (n = 17), and 21 weeks (95% CI: 11 weeks, upper limit not yet reached) for the cabozantinib group (n = 14). The hazard ratio of 0.13 (95% CI: 0.03-0.50) strongly favored the cabozantinib arm and corresponds to an 87% reduction in the risk of disease progression for subjects treated with cabozantinib compared with placebo ($P = 0.0007$). The overall median PFS from Day 1 of starting cabozantinib treatment, excluding subjects randomized to placebo, was 29 weeks and appeared to be independent of prior docetaxel treatment.

Ovarian Cancer Cohort (N = 70)

The majority (93%) of enrolled subjects had the ovary as primary disease site, and 79% had serous cell carcinoma differentiation. Forty-nine percent of enrolled subjects were considered platinum refractory/resistant, defined as a platinum-free interval of 6 months or less. More than half of the subjects (57%) had received ≥ 2 prior lines of platinum-based chemotherapy, 31% had received pegylated liposomal doxorubicin or topotecan, and 10% had received prior VEGF pathway inhibitors. The overall DCR at Week 12 was 53%. Two of 11 subjects (18%) with platinum refractory disease, defined as a platinum-free interval of < 1 month, achieved a confirmed response (one CR and one PR). Five of 23 subjects (22%) with platinum-resistant disease, defined as a platinum-free interval of 1-6 months, achieved a PR. Ten of 36 subjects (28%) with platinum sensitive disease, defined as platinum-free interval > 6 months, achieved a PR. The DCR at Week 12 for the platinum-refractory group was 36%, for the resistant group 39%, and for the sensitive group 67%. A total of 37 patients experienced reductions in the ovarian cancer tumor marker CA125, including 8 with decreases greater than 50%. There was no consistent concordance between CA125 changes and tumor regression. At the time point of the analysis, the median duration of response was not reached with 36 weeks of median follow-up (Buckanovich et al. 2011).

Melanoma Cohort (N = 77)

Fifty-four (70%) of the enrolled melanoma subjects had advanced cutaneous/mucosal melanoma and 23 (30%) had advanced primary ocular disease. BRAF mutation was detected in 17 (32%) of subjects. The majority of patients (87%) had 0-2 lines of prior therapy and 13% had 3 or more lines of therapy. The overall DCR at Week 12 was 47%. Regression of measurable soft-tissue disease was observed in 39 of 65 (60%) of subjects with at least one post-baseline tumor assessment. During the Lead-In Stage, the first 12 weeks of the study, a cPR was observed in 4 subjects. Tumor regression appeared to occur regardless of BRAF mutational status. Two out of 2 patients with bone metastases followed by bone scan experienced partial resolution of bone lesions. One patient with symptomatic bone metastases following treatment with ipilimumab experienced relief of bone pain on cabozantinib and remains on study with stable disease for more than 6 months. Of the 77 enrolled subjects, including those potentially randomized to placebo, 27% remained on study at 6 months.

NSCLC Cohort (N = 60)

The majority (93%) of enrolled subjects had Stage IV disease at diagnosis, and 7% had stage III disease. Seventeen (28%) subjects had squamous cell carcinoma differentiation, and 43 (72%) had adenocarcinoma or other histologic subtypes. Half of the subjects had 0-2 lines of prior therapy, and the other half had 3 or more lines of prior therapy. Prior therapies included anti-VEGF pathway therapy (32%) and anti-EGFR therapy (42%). The overall DCR at Week 12 was 40%. Six subjects (10%) achieved a cPR. Tumor regression appeared to occur regardless of either EGFR or KRAS mutational status. Forty percent of subjects in the cohort remained on study greater than 3 months.

HCC Cohort (N = 30)
All enrolled subjects were Child-Pugh Class A, and 19 (63%) had evidence of extrahepatic spread. The majority of subjects (93%) had 0-1 line of prior therapy and 7% had 2 or more lines of therapy. Nearly half (47%) of subjects had been treated previously with sorafenib. The overall DCR at Week 12 was 73%. Regression of measurable soft-tissue disease per mRECIST was observed in 22 of 27 (81%) subjects with at least one post-baseline tumor assessment. Four subjects (15%), including subjects with and without prior sorafenib therapy, achieved a cPR. Nine of 16 (56%) subjects who had AFP levels ≥ 20 ng/mL at baseline experienced ≥ 50% reduction in AFP. Of the 30 subjects in the cohort, 47% remained on study greater than 6 months.

Breast Cancer Cohort (N = 20)
The majority (90%) had invasive ductal carcinoma differentiation. Breast tumor tissue was positive for estrogen and progesterone receptors (ER+/PR+) for 15 of 20 enrolled subjects (75%) and positive for HER2 (HER2+) for 3 subjects (15%). Eighty-five percent had three or more lines of therapy, and 40% had been treated previously with anti-VEGF pathway therapy. The overall DCR at Week 12 was 45%. Regression of measurable soft-tissue disease was observed in 15 of 16 (94%) of subjects with at least one post-baseline tumor assessment. During the Lead-In Stage, the first 12 weeks of the study, a cPR was observed in 2 subjects. Two of 3 subjects with bone metastases followed by bone scan experienced partial resolution on bone scan accompanied by symptomatic pain relief.

SCLC (N = 21), Pancreatic Cancer (N = 20), Gastric/GEJ Cancer (N = 21) Cohorts
Lower DCRs at Week 12 were observed in SCLC (38%), pancreatic cancer (35%), and gastric/GEJ cancer (33%). Confirmed partial tumor responses were observed in SCLC (1) and gastric/GEJ cancer (1).

Translational Medicine
Genotyping data in the XL184-001 study suggest the absence of a correlation between RET mutations and either clinical response or time on study. In an ongoing analysis in the XL184-201 study, genotyping analysis of several genomic alterations frequently found in GB revealed that none appear to confer resistance to cabozantinib.

Data from subjects enrolled in ongoing clinical studies demonstrated statistically significant changes in plasma biomarkers such as sMET and sKIT. Analysis of serial hair and/or skin samples revealed substantial inhibition of the phosphorylation of cabozantinib targets such as MET, RET, and KIT, as well as of downstream signaling molecules AKT and ERK, following administration of cabozantinib.

2.2 Study Disease
Neuroendocrine tumors, which include carcinoid tumors and pancreatic neuroendocrine tumors, are relatively uncommon, comprising only approximately 1-2% of all malignancies. However, this assertion has been revisited in recent years, with the most recent SEER database reporting an annual incidence of over 5 per 100,000 [1]. When patients with neuroendocrine tumors present with surgically resectable disease, the prognosis is excellent, but unfortunately, a substantial fraction of patients with neuroendocrine tumors either present with or develop metastatic disease

that is not amenable to curative approaches. In these patients, cytotoxic chemotherapy has been of limited efficacy and counterbalanced with substantial toxicities. A variety of other agents have been attempted, including somatostatin analogs such as octreotide, tyrosine kinase inhibitors, such as sorafenib [2] and sunitinib [3], VEGF antagonists, such as bevacizumab [4], and mTOR inhibitors such as temsirolimus [5], and everolimus [6]. Somatostatin analogs are generally administered to patients for symptomatic benefit, but have not generally resulted in radiographic responses. A strategy of angiogenesis inhibition in particular is compelling in neuroendocrine tumors given the highly vascularized nature of neuroendocrine tumors [7-9]. Well-differentiated neuroendocrine tumors have a higher microvessel density than poorly differentiated neuroendocrine tumors [10, 11]. In addition, pancreatic endocrine tumors also display platelet-derived growth factor receptors and stem-cell factor receptor (c-kit) [12, 13].
Metastatic pancreatic neuroendocrine tumors have been demonstrated to express MET, and in one small study, 33% of metastatic pancreatic endocrine tumors versus only 17% of non-metastatic neuroendocrine tumors expressed MET. Greater than 50% of tumors metastatic to lymph nodes or liver expressed MET [14].

The data from clinical trials to date demonstrate possible clinical benefit of antagonism of the VEGF pathway in neuroendocrine tumors. In a Phase II trial of 44 patients with metastatic carcinoid tumors, the use of bevacizumab was associated with a response rate of 18% and progression-free survival (PFS) of 95% versus a response rate of 0% and PFS of 68% for patients receiving interferon-based therapy [4]. Similarly, the use of sunitinib, a multitargeted tyrosine kinase inhibitor that includes activity against VEGF and KIT, in a Phase II trial of 109 patients with advanced neuroendocrine tumors demonstrated partial responses of 16.7% and 2.4% in pancreatic neuroendocrine and carcinoid tumors, respectively. Stable disease was achieved in 83% of patients with carcinoid and 68% of patients with pancreatic neuroendocrine tumors [3]. In a recent published Phase III trial of sunitinib versus placebo restricted to patients with pancreatic neuroendocrine tumors, the objective response rate was 9.3%, but median progression free survival was more than doubled compared to patients treated with placebo (11.4 months versus 5.5 months) [15].

2.3 Rationale

The antitumor activity of prior VEGF-directed therapies with bevacizumab and sunitinib, along with the currently limited treatment options for patients with neuroendocrine tumors make the identification of further agents with activity in patients with carcinoid and pancreatic neuroendocrine tumors a high priority. We propose to study cabozantinib, which is known to inhibit both VEGF, MET, and KIT receptors, in patients with neuroendocrine tumors. Carcinoid tumors and pancreatic neuroendocrine tumors have demonstrated markedly different response rates in prior trials of sunitinib and everolimus, and a recently published consensus of the national cancer institute recommend evaluation separately in clinical trials [16]. Therefore, we propose enrolling two cohorts of patients, one with carcinoid tumors, and one with pancreatic neuroendocrine tumors. We plan to treat patients with cabozantinib 60 mg (free base weight) per day. This dose was selected based on the dose reductions necessary in the XL184-203 clinical trial, where over half of patients required a dose reduction to 60 mg. Our primary endpoint will be overall response rate, and secondary endpoints will include progression-free and overall survival. Patients will be enrolled at the Massachusetts General Hospital Cancer Center and the Dana Faber Cancer Institute.

2.4 Correlative Background

There are ongoing efforts to identify biomarkers to predict response to various cancer therapeutics and allow for better matching of potentially toxic therapies with patients most likely to respond [17]. In particular, predicting and assessing response to antiangiogenic agents is vitally important. No validated biological markers (or biomarkers) currently exist for appropriately selecting patients with cancer for antiangiogenic therapy. We also lack biomarkers able to identify escape pathways that should be targeted after tumors develop resistance to a given antiangiogenic agent. A number of potential systemic, circulating, tissue and imaging biomarkers have emerged from recently completed phase I–III studies [17]. Some of these are measured at baseline, for example VEGF gene polymorphisms, soluble VEGF receptor 1 (sVEGFR1), while others are measured during treatment (such as hypertension, MRI-measured Ktrans, circulating angiogenic molecules or collagen IV); all are mechanistically based. Some of these biomarkers might be pharmacodynamic, for example, increase in circulating VEGF, placental growth factor (PlGF), while others have potential for predicting clinical benefit or identifying the escape pathways, for example, stromal-derived factor 1α (SDF1α) or Interleukin 6. Most biomarkers are disease and/or agent specific and all of them need to be validated prospectively. These need to be explored in larger patient cohorts and in a disease– and agent-specific manner. In rectal cancer patients, we previously found that sVEGFR1 may be a predictive biomarker of response and toxicity for bevacizumab with radiation and chemotherapy [18, 19]. In addition, we found that bevacizumab therapy alone increased the cancer cell expression of SDF1α and its receptor CXCR4 [20]. Moreover, high plasma SDF1α concentration during treatment was significantly associated with development of distant metastases [21]. Bevacizumab induced a sustained elevation in circulating plasma VEGF and PlGF, transiently increased sVEGFR2 and IL-6, and decreased sVEGFR1 [18]. The change in plasma PlGF (after bevacizumab alone) correlated with pathologic response after treatment, and circulating VEGF and IL-6 (after bevacizumab with chemoradiation) showed association with nodal disease status after treatment [18]. We found that some of these biomarkers were common across disease types and antiangiogenic agent types. For example, bevacizumab increased VEGF, PlGF and sVEGFR2 in sarcoma and ovarian cancer patients [22, 23]. On the other hand, while anti-VEGFR tyrosine kinase inhibitors such as cediranib, sunitinib and sorafenib also increased circulating PlGF and VEGF levels in brain tumor, hepatocellular carcinoma and sarcoma patients, respectively, they decreased sVEGFR2 and increased SDF1α in all cases [20, 24-26]. Similar to rectal cancer, increases in circulating SDF1α correlated with a poor outcome after anti-VEGFR therapy [20, 24-26]. These hypotheses-generating data from these exploratory studies need to be confirmed in further studies of anti-VEGF agents. We have previously have evaluated a battery of biomarkers after bevacizumab treatment in patients with various types of cancer: rectal carcinoma [18, 19, 21, 27-30], sarcoma [23], ovarian carcinoma [22], lung carcinoma [31], and Schwannoma [32], as well as in breast cancer (trial ongoing, #DFCI 07-130). These biomarkers have been evaluated in more than a dozen trials of anti-VEGFR tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, vatalanib, cediranib, vandetanib)[20, 24-26, 33-35]. In study XL184-001, a Phase I study of cabozantinib administered to subjects with advanced malignancies, a preliminary analysis of samples of 14 subjects revealed statistically significant change in VEGF-A and sVEGFR2 levels.

Functional imaging may also be a useful tool for the evaluation of treatment response. In particular, functional CT has been used at MGH to assess changes in tumor perfusion parameters such as blood flow, blood volume, mean transit time and permeability surface area following therapy in rectal cancer, where both blood flow and PS product as measured by dynamic CT were significantly decreased following treatment with a bevacizumab-containing treatment [18]. At MGH, low dose CT perfusion technique has also been utilized in hepatocellular carcinoma, where lower mean transit time was significantly associated with progressive disease. In addition, bevacizumab therapy was associated with decreases in blood flow, blood volume, and permeability surface area product, though only change in mean transit time after bevacizumab therapy correlated with clinical outcome [36]. Functional CT has also been utilized in neuroendocrine tumors, revealing a correlation between decreases in blood flow and volume with anti-VEGF treatment with bevacizumab at day 2 and week 18 [4].

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening and on Day 1 of treatment to be eligible to participate in the study:

3.1.1 Locally unresectable or metastatic, histologically-confirmed, carcinoid or pancreatic neuroendocrine tumor. Tumors must be considered well- or moderately-differentiated. Patients with poorly differentiated neuroendocrine carcinoma are excluded from the study.

3.1.2 A tumor sample is required for enrollment (except for patients diagnosed > 7 years ago).

3.1.3 Must have measurable disease by RECIST criteria

3.1.4 Must have evidence of progressive disease within 12 months of study entry

3.1.5 For patients with carcinoid tumors, patients must have progressed on, be currently receiving, or be intolerant to octreotide therapy. For patients with pancreatic neuroendocrine tumors, the prior or current use of octreotide or somatostatin analogues is permitted, but not required. If the patient is on octreotide, regardless of whether the patient has a carcinoid or pancreatic neuroendocrine tumor, the patient must be on a stable dose of somatostatin analogue for at least two months.

3.1.6 Age ≥18 years

3.1.7 No major surgery or radiation in the prior 4 weeks prior to enrollment

3.1.8 No prior therapy with cabozantinib

3.1.9 ECOG Performance status ≤1

3.1.10 Participants must have adequate organ and marrow function as defined below:

- Absolute neutrophil count > 1,500/mcL
- Platelets > 100,000/mcL
- Total bilirubin </= 1.5X normal institutional limits
- AST (SGOT) and ALT (SGPT) </=2.5x normal institutional limits, or < 5x if liver metastases are present
- Creatinine </= 1.5x normal institutional limits or creatinine clearance >50mL/min

- Urine Protein:Creatinine ratio of <1
- Lipase <1.5X upper limit of normal
- Serum Albumin ≥2.8 g/dl

3.1.11 Sexually active subjects must agree to use medically accepted methods of birth control during the course of the study and for 3 months following discontinuation of study treatments (excluding women who are not of child bearing potential and men who have been sterilized).

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

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 The first dose of study treatment must be at least three weeks since prior chemotherapy, including sunitinib or everolimus.

3.2.2 Major surgery or radiation treatment <4 weeks prior to enrollment. In addition, cannot have received radiation to the thorax or gastrointestinal tract within three months of the first dose of study treatment.

3.2.3 Cannot have received radionuclide treatment within 6 weeks of first dose of study treatment.

3.2.4 High grade or poorly differentiated neuroendocrine tumors

3.2.5 Ongoing immunosuppression with systemic steroids or other immune modulator

3.2.6 Presence of CNS metastatic disease

3.2.7 Uncontrolled hypertension defined by SBP>140 or DBP>90 despite titration of anti-hypertensive medications

3.2.8 No uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia other than chronic atrial fibrillation, or psychiatric illness/social situations that would limit compliance with study requirements. Congestive heart failure or symptomatic coronary artery disease within 3 months prior to enrollment

3.2.9 Cerebrovascular accident within prior 6 months

3.2.10 The subject has a history of clinically significant hematemesis or a recent history of hemoptysis of > 2.5 mL of red blood or other signs indicative of pulmonary hemorrhage or evidence of endobronchial lesion(s).

3.2.11 The subject has a pulmonary lesion abutting or encasing a major blood vessel.

3.2.12 History of pulmonary embolism or deep venous thrombosis within the past six months of the first dose of study treatment

3.2.13 The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or Coumadin-related agents, heparin, thrombin or FXa inhibitors, and antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic Low Molecular Weight Heparin (LMWH) are permitted.

3.2.14 At the time of screening, active peptic ulcer disease or active inflammatory bowel disease (including ulcerative colitis or Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis, or appendicitis.

3.2.15 History of abdominal fistula, gastrointestinal perforation, bowel obstruction, gastric outlet obstruction, or intra-abdominal abscess within six months of study enrollment.

3.2.16 History of GI surgery within the past 28 days.

days. If > 28 days since GI surgery, must have confirmation of complete healing before initiating treatment with study drug.

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

3.2.18 Other clinically significant disorders such as:

i. Active infection requiring systemic treatment
ii. Serious non-healing wound/ulcer/bone fracture
iii. History of organ transplant
iv. Concurrent uncompensated hypothyroidism or thyroid dysfunction
v. History of major surgery within 4 weeks or minor surgical procedures within 1 week before randomization

3.2.19 The subject has a baseline corrected QT interval <500 within 28 days before randomization.

3.2.20 Severely impaired lung function

3.2.21 Concurrent malignancy (other than non-melanoma skin cancer) diagnosed within the past 3 years or any currently active malignancy

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

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

There are no specific provisions for this. Both men and women and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**
3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

1. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.
2. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

Not applicable.

4.4 Registration Process for Other Participating Institutions

Not applicable.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial anti-cancer agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. Participants will sign informed consent and screen for eligibility.

5.1 Pre-treatment Criteria

Subjects must meet eligibility criteria on the first day of treatment, and have completed all required data activities by the first day of treatment.

5.2 Agent Administration

Cabozantinib 60 mg (free base weight) per day will be administered daily and continuously for a cycle length of 28 days. The 60 mg starting dose was derived from the ongoing adaptive randomized discontinuation trial, XL184-203, which used 100 mg per day (free base weight), but over half of patients required a dose reduction to 60 mg. Participants will keep a drug diary to document daily oral dosing of cabozantinib. Subjects will be provided with a sufficient supply of study treatment and instructions for taking the study treatment on days without scheduled clinic visits. After fasting (with exception of water) for 2 hours, subjects will take study treatment daily each morning with a full glass of water (minimum of 8 oz/ 240 mL) and continue to fast for 1 hour after each dose of study treatment. For missed doses, if it has been more than 12 hours since a scheduled dose, patients will be instructed not to take the missing dose. If patients vomit after taking their scheduled tablets, they will be instructed not to take another dose on this day and continue on their regular dosing schedule. If doses are withheld, the original schedule of assessments should be maintained when cabozantinib is restarted. The subject should be instructed to not make up the missed doses and to maintain the planned dosing schedule.

Subjects will be monitored continuously for adverse events through 30 days (+7 days) after the date of the decision to discontinue study treatment. Subjects will be instructed to notify their physician immediately for any and all toxicities. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay, or reduction(s), in their dose in order to continue with study treatment. Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the PI when possible, before a decision is made to modify the dose or to hold dosing temporarily.

5.2.1 Drug formulation – Cabozantinib (XL184)

Composition, Formulation, and Storage

Cabozantinib must be stored at room temperature and inventoried according to applicable state and federal regulations.

Investigational Treatment

Chemical Name: Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt.

Cabozantinib is an L-malate salt. In all studies except XL184-203, cabozantinib doses and capsule strengths are expressed based on the weight of the cabozantinib salt. However, in Study XL184-203, doses and capsule strengths are expressed based on the cabozantinib free base equivalent weight. The new standard for Exelixis is to express the dosing in terms of the free base weight. The difference between capsule strengths based on freebase or the L-malate salt weight (ie, < 2% based on correction for salt equivalent weights) is small relative to the variance in mean exposures in subjects administered the same cabozantinib capsule dose (approximately 40% coefficient of variation for mean AUC), and is therefore considered to be not clinically relevant.

Cabozantinib Tablets
Cabozantinib will be supplied as 20 mg tablets. These tablets are in free-base dosing form. The cabozantinib tablet components and doses are presented in Appendix B.

5.2.2 Availability
Cabozantinib is an investigational agent and will be supplied free-of-charge by Exelixis.

5.2.3 Accountability
Study participants will keep a drug diary to record dosing of cabozantinib. Cabozantinib bottles and any unused drug will be brought back to the research staff for accountability.

5.2.4 Destruction and Return
At the end of the study, unused supplies of Cabozantinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

5.3 General Concomitant Medication and Supportive Care Guidelines

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

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from in vitro studies using CYP-isozyme specific neutralizing antibodies. Preliminary results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4

family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

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

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

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

Other Interactions: A relative bioavailability study in dogs suggests that cabozantinib is unlikely to be affected by drugs that alter gastric pH. In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure.

5.3.2 Use of other cancer treatments on study

The use of octreotide/somatostatin during the study is permitted as discussed in the inclusion criteria.

Other than somatostatin, no other antineoplastic agents will be permitted during this study. No concurrent radiation treatment will be permitted, except for palliation or symptom relief after completion of Cycle 2. The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study.

The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated. See Section 6.

5.3.3 Supportive medications
Other concomitant medications may be given as clinically indicated, including supportive medications for diarrhea, nausea/vomiting, or other supportive medications.

5.3.4 Use of other medications not specified above
No treatment with chronic immunosuppressants (e.g., cyclosporine following transplantation or systemic steroids for treatment of autoimmune disease) will be permitted during this study; however, use of inhalant steroids and steroids given for antiemetic purposes or supportive therapy for brain metastases are permitted.

5.4 Duration of Therapy
Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

Disease progression,
Intercurrent illness that prevents further administration of treatment,
Unacceptable adverse event(s),
Participant decides to withdraw from the study, or
General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up
Subject survival information will be collected, preferably via office visit or telephone contact, every 12 weeks (± 1 week) from the date of last dose of study drug until the subject's death or until the subject is lost to follow-up, or until study closure (approximately 6 months after the last subject terminates treatment).

5.6 Criteria for Removal from Study
Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Jennifer Ang Chan, Pager 42017

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS
Toxicity assessments will be carried out using NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.0) which is available at http://ctep.cancer.gov/reporting//ctc.html).

Subjects will receive cabozantinib orally at a (starting) dose of 60 mg (free base) once daily. In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines below.

6.1 General Guidelines for Treatment Delay, Dose Reduction, or Study Drug Discontinuation for Toxicity

Subjects will be monitored continuously for AEs throughout the study and for 30 days (+ 7 days) after the last dose of study treatment, and for any serious adverse event assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the last dose of study treatment. Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay or reduction(s) in their dose in order to continue with study treatment. Assessment of causality (chronology and confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the principal investigator (PI) when possible, before a decision is made to modify the dose or to hold dosing temporarily.

As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity to avoid dose interrupts and reductions if possible.

Re-escalating study treatment after a dose reduction:

- Subjects may be re-escalated to the previous dose at the discretion of the investigator but not sooner than 2 weeks beyond the resolution to Grade ≤ 1 or to the baseline value of AEs.
- If a subject has been dose-reduced more than once (20 mg qd), dose escalation can only occur to the next dose level (40 mg qd). Further dose escalation to the highest dose level is allowed only if clinically indicated per investigator's judgment.
- If the AEs that previously led to dose reduction(s) recur upon re-escalation, the dose should be reduced again and no further dose escalation will be permitted.

Dose re-escalation is not allowed for dose reduction triggered by neutropenia or thrombocytopenia.

TABLE 6.1 – Dose reductions

Starting dose	1st dose reduction	2nd dose reduction
60 mg (free base weight)	40 mg (free base weight)	20 mg (free base weight)

Note: subjects may be re-escalated to the previous dose at the discretion of the investigator no sooner than 2 weeks beyond resolution (Grade ≤ 1 or to the baseline value [or lower] of AEs).

Subjects who cannot tolerate study treatment at 20 mg (free base) PO will be discontinued from study treatment.

Discontinuation from study treatment:

- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 1 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity.
- The minimum dose of study treatment will be 20 mg (free base) qd. Subjects who cannot tolerate 20 mg qd will have study treatment discontinued.

Additional information for dose delays or dose reductions:

- Dose delays for reason(s) other than AEs related to cabozantinib, such as surgical procedures with no anticancer therapy intent, may be allowed with investigator approval. The acceptable length of interruption will be determined by the investigator and sponsor.

Warnings, Precautions, and Management of Anticipated Adverse Events

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, PPE syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (eg, PE and DVT), hypertension, proteinuria, hemorrhagic events, and rare cases of GI perforation and rectal/perirectal abscess. Arterial thromboembolism (TIA, MI) have been reported rarely.

6.2 Management of Adverse Events

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

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

The reason for treatment delay and reduced dose must be recorded on the CRF.

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

Events triggering permanent discontinuation of cabozantinib:

- Development of Grade 4 thromboembolic events
- Development of an acute MI or any other clinically significant arterial thromboembolic complication.
- Any Grade 4 non-hematologic toxicity, with the exception of Grade 4 asymptomatic amylase or lipase elevation, judged to be related to study medication unless the patient is deriving clinical benefit from cabozantinib. If the patient is deriving clinical benefit from cabozantinib, the toxicity must resolve to Grade ≤1 prior to restarting, and after approval by the investigator, treatment at a reduced dose can be considered.
- Transaminase elevations that are accompanied by evidence of impaired hepatic function (bilirubin elevation > 2xULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury.

- Any Grade 4 neutropenia judged to be related to study medication unless the patient is deriving clinical benefit from cabozantinib. If the patient is deriving clinical benefit from cabozantinib, the toxicity must resolve to Grade ≤1 prior to restarting, and after approval by the investigator, treatment at a reduced dose can be considered.
- Serious and life-threatening bleeding events or recent hemoptysis (≥ ½ tablespoon of red blood).
- Gastrointestinal perforation or gastrointestinal fistula of any Grade
- Grade 3 toxicities that have not resolved to ≤1 within six weeks

General Guidelines for Non-Hematologic and Hematologic Adverse Events
General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 6.2.1 and Table 6.2.2, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders (lipase and amylase elevations), skin disorders (PPE), embolism and thrombus, hypertension, proteinuria, hemorrhage, rectal and perirectal abscess; gastrointestinal perforation and gastrointestinal fistula, wound healing and surgery, and endocrine disorders, refer to the specific subsections below. Guidance for the management of fatigue, anorexia, weight loss, non-gastrointestinal fistula, osteonecrosis of the jaw, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastional disorders and congenital, familial and genetic disorders can be found in the Investigators Brochure.

Table 6.2.1 Management of Study Treatment-Related Non-Hematologic Toxicities

CTCAE Version 4 Grade	Intervention
Grade 1:	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2:	
Grade 2 AEs considered related to study treatment that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2 AEs considered related to study treatment that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Dose reduce • If the AE does not resolve to Grade ≤ 1 or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. • If the AE resolves to Grade ≤ 1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to study treatment which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Add supportive care as indicated • AEs that are easily managed (e.g., correction of electrolytes) with resolution within 24 hours do not require a dose modification unless this is a recurring event, at which time the dose should be reduced. • For AEs that require supportive care, the dose should be reduced or interrupted while supportive care is initiated and optimized. If a treatment interruption is required, then upon resolution to baseline or Grade ≤ 1, treatment should be restarted with the reduced dose.
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction.
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor and only with approval by the sponsor.

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

Table 6.2.2: Management of Hematologic Toxicities

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

ANC, absolute neutrophil count.

Note: Tables 6.2.1 and 6.2.2 do not account for "Transaminase elevation," "Asymptomatic Lipase or Amylase Elevations," "Hand-Foot Skin Reactions," "Hypertension," and "Treatment-Emergent Proteinuria", which are discussed later in the text and have separate reference tables.

Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson et al. 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. When combination therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, a dose reduction and/or dose interruption of cabozantinib should be implemented as described in Table 6.1. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. A dose reduction and/or dose interruption of cabozantinib may be required as described in Table 6.1 if anti-emetic treatment and/or prophylaxis alone is not adequate.

Agents classified as having a high therapeutic index (such as 5-HT3 receptor antagonists, or NK-1 receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or dexamethasone are recommended (Hesketh et al. 2008, ASCO 2006; Roila et al, Annals of Oncology, 2010). Caution is recommended with the use of aprepitant or fosaprepitant and nabilone as cabozantinib exposure may be affected by concomitant administration because aprepitant and fosaprepitant are both inhibitors and inducers of CYP3A4, and nabilone is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as a traumatic cleansing, and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

Hepatobiliary Disorders

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

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

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue study treatment with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.

Grade 2	Continue study treatment with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT > ULN – 3.0 x ULN at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade <3	Continue study treatment with at least twice weekly monitoring of LFTs for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.
Subjects AST or ALT > 3.0 – 5.0 x ULN at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.

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

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

All subjects who develop isolated bilirubin elevations $\geq$ 3 times the upper limit of normal 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 know but, in general have not been associated with clinically apparent sequelae, and no specific interventions is required.. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If asymptomatic grade 3 or 4 elevations recur following retreatment after previous grade 3 or grade 4 asymptomaic lipase or amylase elevation, then treatment must be interrupted again until amylase and lipase levels have resolved to Grade <=1 or baseline. Retreatment must be at a reduced dose; if already at the 20 mg dose level, treatment can resume at 20 mg.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or a reduced dose if resolution occurred within 4 days). Otherwise the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If asymptomatic grade 3 or 4 elevations recur following retreatment after previous grade 3 or grade 4 asymptomaic lipase or amylase elevation, then treatment must be interrupted again until amylase and lipase levels have resolved to Grade <=1 or baseline. Retreatment must be at a reduced dose; if already at the 20 mg dose level, treatment can resume at 20 mg.

Symptomatic Pancreatitis

Pancreatitis	
Grade 1	Continue at current dose level. More frequent monitoring is recommended, including radiographic assessment as appropriate.
Grade 2	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 2 pancreatitis is at the same dose and Grade 2 pancreatitis recurs, then treatment must be interrupted again and till resolution to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was clearly deriving benefit from cabozantinib therapy, treatment may resumed at a reduced dose if agreed to by both the investigatory and the sponsor.

Skin Disorders

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

The onset of PPE is variable with paresthesia (tingling, numbness) being the characteristic initial manifestation, which can be accompanied by slight redness or mild hyperkeratosis. PPE advances with symmetrical painful erythema and swollen areas (edema) on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas.

Aggressive management of symptoms is recommended, including early dermatology referral. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

In the case of study treatment-related skin changes (eg, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

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

Embolism and Thrombosis

In clinical studies with cabozantinib, venous thrombotic events (DVT and PE) have been observed in less than 10% of subjects, and arterial thromboembolic events (MI and TIA) have been reported rarely. In addition, subjects with cancer have a significantly increased likelihood of developing thromboembolic complications (De Groot et al, 2009).

Cabozantinib must be discontinued in subjects who develop Grade 4 thromboembolic events or who develop an acute MI or any other clinically significant arterial thromboembolic complication. In patients who require therapeutic anticoagulation for Grade 2 or Grade 3 thromboembolic events, cabozantinib may be continued as follows: Subjects who develop a Grade 2 or Grade 3 PE and/or DVT should have study treatment interrupted until full anticoagulation is established with low molecular weight heparin (LMWH) (Full anticoagulation with warfarin is not permitted). 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.

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

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking new therapeutic action. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥ 160 mm Hg systolic or ≥ 110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy.

Management of Hypertension Related to Cabozantinib

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

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

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

Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Development and worsening of proteinuria should be monitored by serial urinalysis (qualitative/ semiquantitative assessment by dipstick; quantitative assessment by urine protein/urine creatinine ratio [UPCR], or 24-hour urine protein excretion). When a UPCR exceeds 1 (mg/dL protein / mg/dL creatinine), a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in Table 6.2.3.

Table 6.2.3: Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• Confirm with a 24 hour urine protein excretion within 7 days • If proteinuria of > 1 g/24 hours is confirmed, hold cabozantinib and continue with UPCR monitoring. When UPCR returns to < 1, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until 2 consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

Hemorrhage

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

- Tumor lesions of the lung with cavitations or tumor lesions which invade, encase, or abut major blood vessels of the lung; NSCLC with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. The anatomic location and characteristics of tumor as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions that affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis

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

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ ½ tablespoon of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must immediately be discussed with the sponsor to determine the safety of continuing study 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.

Gastrointestinal perforation and GI fistula
Gastrointestinal perforation and GI fistula have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. To allow for early diagnosis, subjects should be monitored for episodes of abdominal pain, especially if known risk factors for developing GI perforation or fistula (Turnage et al. 2008) are present. Such risk factors include (but may not be limited to) the following:

- 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 use of steroid treatment or non-steroidal anti-inflammatory drugs (Rodriguez et al. 2001, Straube et al. 2009). Constipation, consistent with symptoms of bowel obstruction, should be monitored and effectively managed. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or 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 TFTs in a high number of subjects. In Study XL184-203, 17 of 34 (50%) euthyroid subjects with CRPC developed abnormal thyroid-stimulating hormone (TSH) levels 6 weeks after initiation of cabozantinib treatment (6% showed TSH levels between 5 and 7 mU/L, 44% had TSH > 7 mU/L). The median TSH level at week 6 was 5.2 mU/L (range, 0.02-29.7 mU/L). In a Phase 1 combination study of rosiglitazaone and cabozantinib (XL184-008) to determine the potential for a clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8, subjects with advanced solid tumors (particularly RCC and DTC) are enrolled. Among 11 evaluable subjects, the AE of hypothyroidism was reported in 55% of subjects. Currently available data are insufficient to determine the cause of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

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

Concomitant Medications and Therapies
Anticancer Therapy
If a subject requires additional systemic anticancer treatment, including steroid treatment for prostate cancer subjects, study treatment must be discontinued other than the use of octreotide. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (eg, palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion. Subjects with prostate cancer currently receiving luteinizing hormone-

releasing hormone (LHRH) or gonadotropin-releasing hormone (GnRH) agonists may be maintained on these agents.

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, vitamins, herbal and nutritional supplements, and over-the-counter medications). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically prior to the first dose of cabozantinib. After the first dose of study treatment, at the discretion of the investigator or after the onset of symptoms, treatment (or prophylaxis) with anti-emetic and anti-diarrheal medications may be undertaken per standard clinical practice. Bisphosphonates are allowed if started prior to screening activities or may be initiated during the course of the study to control bone pain with agreement from the sponsor.

Colony stimulating factors (eg, 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.

7. VISIT SCHEDULE AND ASSESSMENTS

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

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 1 days of the protocol-specified date, unless otherwise discussed with the principal investigator.

7.1 Evaluations

7.1.1 Pretreatment evaluation

Tests to be performed within 28 days prior to initiation of therapy:

- Radiologic assessment of tumor burden by CT scan or MRI within 28 days prior to initiation of therapy.
- Chromogranin A and 24 hour urine 5-HIAA if applicable will be measured at baseline.
- Correlative blood samples to be drawn
- Correlative imaging studies with functional CT (if applicable). This may be performed on a subset of consenting patients if funding is obtained, with the testing performed at MGH.

Tests to be performed within 14 days prior to initiation of therapy:

- All patients will be assessed by history and physical examination, including height, weight, vital signs, and performance status within 14 days prior to initiation of therapy.
- Baseline hematologic and chemistry profiles, including CBC with differential, platelets, and serum chemistries: fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, amylase, lipase, and thyroid function testing.
- Urine protein
- Serum pregnancy test for women of childbearing potential
- Electrocardiogram
- Chromogranin A and 24 hour urine 5-HIAA if clinically indicated

7.1.2 Evaluations during treatment performed every cycle

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- Complete metabolic panel, including bilirubin, ALT, AST, albumin, alkaline phosphatase, albumin, total protein, serum glucose, BUN, creatinine, electrolytes including Na, K, Cl, $HC0_3$, Mg, PO4, Ca, uric acid, amylase, lipase, and thyroid function tests.
- CBC with differential
- Correlative samples for assessment of response (note: circulating tumor cells will be every other cycle for Cycles 2,4 and 6, while circulating biomarkers are drawn on Day#1 of every cycle).
- Urine protein

7.1.3 Evaluations during treatment performed on Day#15 of first 3 cycles:

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- Complete metabolic panel, including bilirubin, ALT, AST, albumin, alkaline phosphatase, total protein, serum glucose, BUN, creatinine, amylase, lipase, electrolytes including Na, K, Cl, HC03, Mg, PO4, Ca, uric acid, and urine protein.
- CBC with differential

7.1.4 Evaluations after cycles 2, 4, and 6, then every third cycle (2, 4, 6, 9, 12, 15, 18, etc.):

- Radiologic assessment of tumor burden by CT scan or MRI
- Chromogranin A and 24 hour urine 5-HIAA if clinically indicated
- Correlative imaging with functional CT (optional). A second functional CT scan may be performed on a subset of consenting patients if funding is available that had a functional CT performed prior to initiation of cabozantinib, with the testing performed at MGH.

7.1.5 Post-treatment evaluation

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- ECOG PS
- Complete metabolic panel, including bilirubin, ALT, AST, albumin, alkaline phosphatase, total protein, serum glucose, BUN, creatinine, electrolytes including Na, K, Cl, $HC0_3$, Mg, PO4, Ca, and uric acid.
- CBC with differential
- Radiologic assessment of tumor burden by CT scan (arterial and venous phase required) at the physician's discretion. An additional liver MRI may be used for those patients with isolated liver metastases in whom the CT does not provide accurate information for liver disease. All sites of tumor progression or metastases will be noted

- Progression-free and overall survival will be determined
- Patients who have an ongoing Grade 4 or serious adverse event at the time of discontinuation from study drug treatment will continue to be followed at monthly intervals, until resolution of toxicity to < Grade 2.Correlative samples for assessment of response

7.2 Study Calendar

REQUIRED INFORMATION/EXAMS	Pre- Study	Day 1 of each cycle [a]	Day 15 of each cycle[b]	Restaging[c]	Post-Treatment Follow-up[d]
Informed consent	X				
Medical and Oncologic History	X	X	X		X
Concurrent meds	X	X	X		X
Physical exam (including height, weight, pulse, blood pressure, oxygen saturation)	X[j]	X	X		X
ECOG Performance Status	X	X	X		X
Adverse event evaluation		X	X		X
Archived Tumor Tissue	X[k]				
EKG	X[j]	X[g]			X
LABORATORY STUDIES					
CBC w/differential	X[j]	X	X		X
Bilirubin, ALT, AST, Albumin, Alkaline Phosphatase, Total protein	X[j]	X	X		X
PT, PTT	X	X			
Serum glucose	X[j]	X			X
BUN, creatinine, electrolytes, including Na, K, Cl, HCO3, Mg, PO4, Ca, uric acid, amylase, lipase	X[j]	X	X		X
TSH with reflex T4	X[j]	X			X
Urine protein	X[j]	X	X		X
Chromogranin, Urine HIAA	X[ji]			X[i]	X[i]
HBsAg, HBSb, HB Core Antibody	X[j]				
β-HCG[e]	X[j]				
Correlative Laboratory Samples	X[h]	X[h]			X[h]
RADIOGRAPHIC TESTS Tumor measurements	X			X	
Radiologic evaluation	X			X	
Correlative Imaging	X[f]			X[f]	

a. Screening assessments must occur within 28 days of start of cabozantinib administration. Pre-registration labs may be used for Day#1 of Cycle#1 if obtained within 7 days of starting treatment. For subsequent cycles, labs must be obtained within 48 hours of start of treatment

b. Day#15 evaluations to be performed for first three cycles, after which time, only need evaluations on Day #1

c. Restaging after cycles 2, 4, and 6, then every 3rd cycle (i.e. 2, 4, 6, 9, 12, 15, 18, etc.) until the first of 3 years after study registration, until disease progression, or end of study treatment. All patients will receive an arterial and venous phase Chest/Abdomen/Pelvic CT. A liver MRI with gadolinium may be included at the discretion of the treating physician. Radiographic evaluations will be performed after cycles 2, 4, and 6, then every 3rd cycle (i.e. 2, 4, 6, 9, 12, 15, 18, etc.)

d. For patients who discontinue study treatment prior to tumor progression, physical examination, performance status, chromogranin A, and radiologic imaging studies should be performed upon discontinuation of study at the physician's discretion. Patients who discontinue treatment at the time of tumor progression should be followed every 6 months with physical exam and performance status, with chromogranin A and imaging studies at the discretion of the investigator.

e: Serum pregnancy test (women of childbearing potential)
f: Patients electing to undergo optional correlative functional imaging, if funding is obtained, will be performed prior to treatment with cabozantinib and after two cycles of treatment.
g. Cycle#2, Day#1 only
h. Plasma biomarker analysis will be drawn at baseline, on Day#1 of every cycle, and post-treatment. Circulating tumor cells will be drawn at baseline, Day#1 of Cycles 2,4 and 6, and post-treatment.
i. Chromogranin A and Urine HIAA is to be collected on at baseline and after cycles 2, 4, and 6, then every 3rd cycle (i.e. 2, 4, 6, 9, 12, 15, 18, etc.) if clinically indicated
j. These assessments are required to be performed 14 days prior to initiation of therapy.
k. Due to a lack of funding, archival tissue will not be collected

EKG Assessments

EKG assessments will be performed with standard 12-lead EKG equipment according to standard procedures. Abnormalities in the EKG that lead to a change in subject management (eg, dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs (Section 9).

8. MEASUREMENT OF EFFECT

8.1 Antitumor Effect

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Therasse et al, 2000). RECIST version 1.1 will be used. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response

8.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

8.1.2 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 will be 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, and should be chosen based on their suitability for accurate repetitive measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case 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 LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

8.1.2.1 Complete Response

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

8.1.2.2 Partial Response (PR)

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

8.1.2.3 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 progression).

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

8.1.3 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.

8.1.3.1 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.

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

8.1.3.3 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 later on by the review panel (or study chair).

8.1.3.4 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.

8.1.4 Cytology and Histology

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. These techniques can be used to differentiate between PR and CR in rare cases (for example, 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.

8.1.5 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 Response for this Category Also Requires:**
CR	CR	No	CR	≥ 4 weeks confirmation*
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks 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 weeks from baseline*
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

*Only for non-randomized trials with response as the 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., Not-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

8.1.6 Guidelines 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.

8.1.6.1 Clinical Lesions

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

8.1.6.2 Chest X-ray/Ultrasound

Ultrasounds should not be used to measure lesions. 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. Chest radiographs may be used as a method of measurement in addition to MRI of the abdomen, if the primary disease is not in the chest, and if there is a concern about radiation exposure due to CT.

8.1.6.3 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. When both CT and liver MRI are used to evaluate liver disease, the MRI will serve as the imaging method to evaluate the size of the lesions within the liver; in this instance, the CT will be used to measure the size of the lesions outside of the liver.

8.1.6.4 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.

8.1.6.5 Endoscopy and 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.

8.1.6.6 Tumor Markers
Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.1.7 Confirmation Measurement/Duration of Response
8.1.7.1 Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 6 weeks.

8.1.7.2 Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are met for CR/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 complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

8.1.7.3 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.

8.1.8 Progression-Free Survival
Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression. This will be assessed as a secondary endpoint in the expansion cohort treated at the recommended phase 2 dose or MTD.

8.1.9 Response Review
Central review of scans will be performed using the Tumor metrics Core.

8.2 Translational Medicine Assessments

This study will collect samples for translational medicine assessments in all enrolled subjects. Sample types include whole blood, plasma, and tumor tissue. Most of the tumor samples are expected to be archival tissue. The sponsor or designee may retain anonymized leftover samples (eg, blood, tumor, DNA) for possible future analyses beyond the end of the study to elucidate further disease subtypes, drug response and toxicity, and possibly to identify new drug targets and additional biomarkers of response to study drug. Samples will be archived according to Food and Drug Administration (FDA) regulations, EMEA's Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007), and will not carry personal identification (eg, Social Security number or name). The samples will be destroyed after 15 years or earlier if requested by the subject unless already anonymized prior to the request.

8.2.1 Pharmacodynamic Assessments

Unless prohibited by local regulations, blood samples will be collected and processed into plasma for all subjects for potential analyses of cabozantinib mechanism of action based pharmacodynamic biomarkers (eg, sMET, HGF, VEGF-A, PlGF, sVEGFR2, sKIT) as well as disease specific markers. Additional exploratory studies may be performed to characterize disease subtypes and potential biomarkers of response or resistance. Analyses may include but are not limited to quantification and genotyping of circulating plasma DNA, evaluation of micro RNAs, and analyses of additional soluble markers. Pharmacodynamic plasma samples will be collected at the time points outlined in Study Calendar (Section 7.2).

8.2.2 Tumor Samples and Analyses

Tumor sample requisition is required for enrollment. Any subjects diagnosed ≥7 years prior to the date of screening with no additional tumor tissue collected in the last 7 years are excluded from this requirement, but efforts should be made to obtain samples if possible. Archival tumor tissue slides (a minimum of 10 consecutive unstained sections of 4-10 microns if available) or a tumor tissue paraffin block will be requisitioned for shipment to a central laboratory. In rare cases, frozen tissue may also be provided. Alternatively, a new biopsy may be obtained before the first dose of cabozantinib. Fine needle aspirates may also be acceptable and collection of tumor fluid samples (confirmed as malignant by a cytopathologist) may be considered on a case by case basis. Tumor analyses may involve evaluation of the signaling pathways related to cabozantinib targets (eg, VEGFR, MET, KIT, RET) and include methods such as genotyping, fluorescence in situ hybridization (FISH) and/or Immuno-histochemistry (IHC). Mutation and/or amplification status of disease-specific tumor-promoters or suppressors may also be determined to characterize the potential impact on response or resistance to cabozantinib (eg, HER2, EGFR, KRAS, NRAS, BRAF, PTEN, PIK3CA, TP53, GNAQ, CDKN2A). Broader genome-wide copy number and mutation profiling may also be conducted. For paired tumor biopsies pharmacodynamic markers such as pMET/MET, pVEGFR2/VEGFR2, pERK/ERK, pAKT/AKT and pKIT/KIT may also be analyzed by IHC. In addition, samples from bone or other tissues may be used to analyze disease-specific markers. Exploratory analyses of potential biomarkers of cabozantinib activity (circulating angiogenic and inflammatory biomarkers VEGF, PlGF, sVEGFR1, bFGF, IL-1β, IL-6, IL-8, and TNF-α and sVEGFR2 and SDF1α may be performed by measuring proteins in the plasma at baseline and on days 1 and 15 post-treatment for the first three cycles, day 1 beyond cycle 3, and at progression in patients with advanced neuroendocrine

tumors. Plasma analysis will be carried out for with samples run in duplicate, using established protocols in a previous study of bevacizumab in Mullerian carcinoma [22]. Blood-circulating cells may be enumerated in fresh samples using a standard flow cytometry protocol. Due to funding, DFCI and MGH will not be collecting archival tissue.

8.2.3 Circulating Biomarkers

8.2.3.1 Plasma Biomarker Analysis

Plasma samples may be analyzed for potential biomarkers using multiplexed enzyme-linked immunosorbent assay (ELISA) kits (96-well plates, 4-10 analytes) or single cytokine ELISA (for analytes unavailable in multiplex, e.g., collagen IV, SDF1α). Using these technology, we will be able to assess VEGF family members and their soluble receptors, and collagen IV, SDF1α, bFGF, sICAM-1, sVCAM-1, PDGF-C, PDGF-B, thrombospondin-1, Ang1, Ang2, IL-1, IL-6, IL-8, and TNF-α. This broad array of proteins to be tested will permit complete evaluation of the most promising known angiogenic biomarkers.

8.2.4 Peripheral blood will be collected for CTC analysis only for patients being treated at Massachusetts General Hospital using the Herringbone-Chip microfluidic platform, as described below. Samples will be collected prior to starting on study, followed by Day 1 of cycles 2, 4, and 6. CTC analyses will be performed in the laboratory of Dr. Daniel Haber. Two 10 mL samples of peripheral blood will be collected into vacutainer tubes (Becton-Dickinson) containing the anticoagulant EDTA. Samples will be processed through the HB-Chip within 6 hours of collection, according to previously established protocols.

Briefly, a 5 mL aliquot of blood will be placed into an air-tight conical tube on a rocker assembly, and approximately 4 mL of blood will be pneumatically driven through the HB-Chip at a flow rate of 1.5-2.5 mL/hour. The HB-Chip will then be flushed with 2.5 mL of phosphate-buffered saline at 2.5 mL/hr to remove nonspecifically bound cells. CTCs on the HB-Chip will be fixed, permeabilized, and stained with antibodies. Captured CTCs will then be identified and enumerated using the automated detection system.

8.2.4.2 Blood collection criteria

8.2.4.2.1 Blood Collection Time Points

Blood samples will be obtained from each participant prior to imaging at each time point as indicated in the study calendar.

8.2.3.2.2 Confidentiality

The confidentiality of the participant's identity will be maintained. All collected information will be protected per federal regulatory guidelines. Access to study data will be limited to the staff working on the study. All computer data will be maintained in a manner consistent with Title 21 Code of Federal Regulations Part 11 (21 CRF Part 11). In addition, access to the data management system will be limited to designated staff through use of individualized, confidential login ID and password. Designated staff will not share login IDs or passwords.

The data from this study will be maintained until 10 years following completion of the study or until the data are no longer required for research. Data will be destroyed as required by the Record Retention Policy and federal regulatory guidelines. Human research subjects are protected in accordance with Title 45 CRF Part 46 and Title 21 CFR Part 50. HIPAA regulations should be followed according to institutional standards.

8.2.3.2.3 Informed Consent

Human research subjects are protected by informed consent procedures in accordance with Title 45 CFR Part 46 and Title 21 CFR Part 50. The Biomarker consent component of the institution-specific, IRB-approved informed consent form grants permission for study investigators to request and obtain blood and blood fractionates, and to use those samples for research involving molecular studies on the development of cancers and/or for other diseases.

All participants will already have provided a written consent for the collection of blood for this biomarker assessment using the institution-specific, IRB-approved informed consent form at the time of enrollment. If blood collection was not included in the original institution-specific, IRB-approved informed consent form, please inform the Protocol Development and Regulatory Compliance department and refer to your local IRB and institutional policy for further guidance.

8.2.3.3 Blood Collection Process

Each participant will have 2 vials of blood (~8 mL each) collected at the time points listed in the study calendar, with the exception of baseline, Day#1 of Cycles 2,4,6, and post-treatment, at which times an addition two 10ml vials of blood will be collected for CTC analysis. The blood must be processed and stored within 30-45 minutes after collection.

8.2.3.3.1 Materials and Labeling of Blood Tubes and Cryovials

All labels will have space for sites to provide the following information:

- Participant study number
- Participant initials
- Time point when sample was collected
- For the blood tubes, a “BL” and for the plasma cryovials, a “PL” to distinguish which label should be used for each tube.

The site will be responsible for obtaining the appropriate tubes for the blood and plasma specimens. The list of supply options are as follows:

For Blood Draw Tubes (3 Options)

1. SARSTEDT Monovette® EDTA KE (9 mL), Part # 02.1333.001; or
2. Becton-Dickinson Vacutainer™ K2E (10 mL), Part # 367525; or
3. Greiner Bio-One Vacuette® K3E EDTA K3 (9 mL), Part # 455036; and

For Plasma Cryovials (1 Option)

1. Nunc, Internally Threaded Cryotube, (3.6 mL vials), Fischer Scientific, Part # 12-565-162N.

8.2.3.3.2 Blood Draw and Centrifugation

- Prior to the blood draw, the blood vacutainer should be pre-cooled by placing tube in a bucket with wet ice.
- Directly from the participant's IV line, draw the 2 vials of blood using 2 pre-labeled blood vacutainer tubes.
- Record time of blood draw on Blood Processing Form (BL).
- Immediately invert the blood tube several times to ensure proper mixing with the preservative.
- Place the blood tube in a bucket filled with wet ice.
- Centrifuge the blood tube at 700*g* (2000rpm) for 20 minutes at 4°C with no break at the end of centrifugation for plasma extraction.
- Using a sterile pipette, pipette the top clear layer (careful not to disturb the bottom red layer) and aliquot equally into 3 pre-labeled 1.8 mL Nunc cryovials.
- Visually check the plasma for hemolysis.
    - If the plasma appears to be yellow and clear, please proceed with processing the plasma and record the observation on the BL form.
    - If the plasma appears to be dark red, please discard the plasma and sign and date the BL form.
- After the plasma has been extracted, check the red blood cells by sticking two wooden applicator sticks in the tube and observe the sticks for clots. Record if there was clotting observed, check yes or no on the Blood Processing Form (BL).
- Record numbers of vials on Blood Processing Form (BL).
- Immediately store the cryovials into a -80°C freezer*.
- Record time of freeze, location of the vials (i.e., freezer number, shelf, box number, and room #, as applicable) on the Blood Processing Form (BL).

* If a -80°C freezer is not available on site, the plasma specimens should be shipped to the core facility on dry ice the same day as processing. See Section 4.0 for shipping procedures

8.2.3.3.3 Labeling and Storing Specimens

For tracking purposes, each specimen and its associated forms should be labeled with the site number and case number. All cryovials should be stored in a monitored -80° C freezer. A separate freezer box should be set a side for the storage of all the plasma vials. They will be shipped in bulk to the testing core facility at completion of study.

8.2.3.3.4 Shipping Specimens to Core Facility

When blood collection has been completed for all participants and after the participants go off trial the plasma samples should be shipped to the Steele Laboratory at Massachusetts General Hospital on dry ice in a Styrofoam box. The Styrofoam container should be packed with at least 7 pounds of dry ice, and make sure the top is completely covered with dry ice. Seal the Styrofoam container within a tight-fitting cardboard shipping box. A copy of the Plasma Shipping (PS) Form for each set of samples should be placed within a separate zip-lock plastic bag and placed on top of the Styrofoam container lid before the external shipping box is sealed.

If the site does not have –80°C storage capability, the plasma samples should be sent to the Steele Laboratory at Massachusetts General Hospital after the blood has been processed. The Styrofoam container should be packed with at least 2 inches of dry ice on the bottom, and completely covered on the top with an additional 2 inches or more of dry ice. Seal the Styrofoam container within a tight-fitting cardboard shipping box. A copy of the Plasma Shipping (PS) Form for each set of samples should be placed within a separate zip-lock plastic bag and placed on top of the Styrofoam container lid before the external shipping box is sealed.

If the site does not have facilities and trained personnel for plasma separation, the blood samples should be shipped to the Steele Laboratory at Massachusetts General Hospital with cold packs in a Styrofoam box within 24 hours (DO NOT FREEZE). Seal the Styrofoam container within a tight-fitting cardboard shipping box. A copy of the Plasma Shipping (PS) Form for each set of samples should be placed within a separate zip-lock plastic bag and placed on top of the Styrofoam container lid before the external shipping box is sealed.

Specimens should be shipped Monday to Wednesday only by overnight FedEx to the Testing Core Facility with the original Sample Submission Form (web site | Protocol 6689 Forms). On the day of shipment, the study coordinator will notify the Testing Core Facility via e-mail at sylvie@steele.mgh.harvard.edu or christina@steele.mgh.harvard.edu or FAX (617-724-5841, ATTN: S. Roberge or C. Koppel) so they know to expect the upcoming shipment. Include the estimated date of arrival and the FedEx tracking number.

NOTE: The subject line of the e-mail/FAX should include the following so that the Testing Core Facility staff can distinguish plasma specimens sent by the sites.

Plasma Specimen Shipment--Site Name
Upon receipt of specimens, the Testing Core Facility will reconcile the materials and notify the site study coordinator of missing specimens, damaged specimens, or any concerns to be addressed.

8.2.3.4 Shipping Materials and Process

The appropriate shipping materials for specimens are the following:

- Storage boxes for plasma tubes (Fisherbrand, 5 3/4" x 5 3/4" x 4 7/8", Part # 03-395-01, and dividers, Part # 03-395-11)
- Large size zip-locked bags
- Multi-purpose insulated bio-shippers (Thermosafe Bio-Shippers; dimensions 14" x 10" x 14")
- Biohazard bags
- M3 carton sealing tape
- Shipping labels to indicate: "Notice: Keep Frozen" use only for **Dry Ice** shipments, Upright arrows, "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650", and "Class 9 – Dry Ice" label; and "Keep Refrigerated" use only for **Cold Pack** shipments.
- Dry ice or Cold Packs

The packing process for dry ice shipments includes the following:

- Place all plasma tubes in storage freezer boxes, tape the sides of the boxes.
- Place one freezer box, each separately, in a large zip-locked bag.
- Pack the Styrofoam container with at least 7 pounds of dry ice.
- Place the bagged freezer boxes in the middle of the bio-shipper. (You can fit as many as the box allows).;
- Pack the Styrofoam container with an additional dry-ice on the top of the boxes to cover the top.
- Place a copy of the Plasma Shipping Form (PS) for a single participant inside one biohazard bag, in the form slot (use as many forms/bags as necessary to cover the contents of the box to be shipped).
- Close the lid, place all bagged shipping forms on top of the lid, and seal the shipping container with tape.
- Maintain a copy of the transmittal log at the site.

The packing process for cold pack shipments includes the following:

- Place all blood tubes in storage freezer boxes, tape the sides of the boxes
- Place one freezer box, each separately, in a large zip-locked bag.
- Place the bagged freezer boxes in the middle of the bio-shipper (you can fit as many as the box allows)
- Pack the Styrofoam container with 4-6 cold packs surrounding the boxes with the blood tubes.
- Place a copy of the Plasma Shipping Form (PS) for a single participant inside one biohazard bag, in the form slot (use as many forms/bags as necessary to cover the contents of the box to be shipped).
- Close the lid, place all bagged shipping forms on top of the lid, and seal the shipping container with tape.
- Maintain a copy of the transmittal log at the site.

8.2.3.4.1 Labeling Shipping Containers

Label each shipping container with the FedEx shipping label to include the following:

1. The study coordinator's return address.
2. The Testing Core Facility address:

ATTN: Sylvie Roberge or Christina Koppel
MGH, Cox-734
100 Blossom St.
Boston, MA 02114
Phone: (617) 726-8143 or (617) 724-1353
Fax: (617) 724-5841
Pager: 14082
Email: sylvie@steele.mgh.harvard.edu or christina@steele.mgh.harvard.edu

1. "Notice: Keep Frozen", "Class 9 – Dry Ice" stickers or "Keep Refrigerated", Upright arrows, and "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650".

8.2.3.4.2 Summary Shipping Task List

The following summarizes the tasks to be completed by the site for a scheduled shipment:

- Prepare transmittal paperwork and retain copies at the site.
- Send a notification e-mail or FAX to the Testing Core Facility listing the items being shipped, including: the FedEx tracking number, total number of plasma tubes in the shipment, and the expected date of arrival. Please note "**Specimen Shipment—Site Name**." in the e-mail or FAX 'Subject' line.
- Pack the plasma specimens according to instructions above.
- Label each shipping container with the FedEx shipping label and affix all appropriate shipping labels.
- Maintain a copy of the transmittal log at the site.

8.2.4 Correlative Imaging

Pending availability of funding, dynamic computed tomography (CT) scans may be offered to all patients with lesions that are at least 2 cm in largest diameter before the first cycle and following the second cycle of cabozantinib. Functional CT will be performed on a 64-slice multidetector row CT scanner (Volume CT, GE Healthcare, Piscataway, NJ). Data will be analyzed on a workstation (Advantage Windows, GE) using commercially available CT perfusion 3.0 software, which implements a deconvolution approach to calculate regional blood flow, blood volume, and permeability-surface area (PS) product. Multiple, non-overlapping regions of interest (ROI) will be drawn over the tumor for each of four 10 mm slices (4 cm of volume) and blood perfusion values will be obtained.

8.2.5 Pharmacogenetic Blood Sample

Unless prohibited by local regulations, a blood sample (collected pre-dose on Week 1 Day 1) may be utilized for genotyping/single nucleotide polymorphism analysis to correlate genetic variation with safety and tolerability or with response to cabozantinib. This may include a genome-wide analysis. The sponsor or designee may retain anonymized DNA samples for future pharmacogenetic analyses beyond the end of the study. The sample will be archived according to FDA regulations, EMEA's Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007), and will not carry personal identification (eg, Social Security number or name). The samples will be destroyed after 15 years or earlier if requested by the subject unless already anonymized prior to the request.

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been given an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Pre-existing medical conditions that worsen during a study should be recorded as AEs.

All untoward events that occur after informed consent through 30 days after the last dose of study treatment are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

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

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause.
- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (eg, evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

Serious Adverse Events

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

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

1. Results in death.
2. Is immediately life-threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity.
5. Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.
6. Is a congenital anomaly or birth defect.
7. Is an important medical event (IME). Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of Serious Adverse Event. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

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

- This report must be submitted by the study site to Exelixis or designee within 24 hours, even if it is not felt to be drug related. Email: drugsafety@exelixis.com; Fax 650-837-7392
- The investigator agrees to provide supplementary information requested by the Exelixis Drug Safety personnel or designee.
- Pregnancy, although not itself an SAE, should also be reported on an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

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

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

The final MedWatch Form must be submitted by the study site to Exelixis at the time of submission to the FDA to allow Exelixis time to cross-report to Exelixis' IND. Email: drugsafety@exelixis.com; Fax 650-837-7392

Other Safety Considerations
Laboratory Data
All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

Pregnancy
If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

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

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

STATISTICAL CONSIDERATIONS
Analysis Population

Safety Population
The safety population will consist of all subjects who receive any amount of study treatment.

Safety Analysis
Safety will be assessed by evaluation of AEs. All safety analyses will be performed using the safety population.

Adverse Events
Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity/ grade and relationship to study treatment will be assessed by the investigator. Severity/ grade will be defined by the National Cancer Institute (NCI) CTCAE v. 4.0. Listings of AEs will be provided.

10. DATA AND SAFETY MONITORING

10.1 Data Reporting

10.1.1 Method
The QACT will collect, manage, and monitor data for this study.

10.1.2 Data Submission
The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason

Form	Submission Timeline
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

10.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all Grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

10.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

11. REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

11.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6) www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

11.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

11.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

11.6 Multi-center Guidelines

N/A.

11.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

12.1.1 Primary Endpoint

The primary efficacy endpoint is the objective response rate (ORR). ORR is defined using the RECIST criteria as the proportion of subjects with a confirmed CR or confirmed PR. The point estimate of the ORR with a 90% confidence interval based on the exact binomial distribution will be presented.

12.1.2 Secondary Endpoints

12.1.2.1 Progression-free survival will be defined as the time from administration of the initial dose of cabozantinib to evidence of radiographic progression as defined by RECIST criteria or death from any cause without evidence of disease progression, whichever occurs first. Cases with incomplete follow up or without adequate disease evaluations will be censored at date last documented to be progression free. Kaplan Meier estimates of progression-free survival rates will be calculated along with their corresponding 95% confidence intervals. Cox proportional hazards regression modeling of PFS will be used to assess the effect of cabozantinib on progression-free survival while controlling for other confounders. Overall survival determined from the time of drug administration to time of death.

12.1.2.2 Overall survival will be defined as the time from administration of the initial dose of cabozantinib until death from any cause.

12.1.2.3 Biologic correlative studies of target inhibition (see above)
All tissue and circulating biomarkers will be correlated with clinical outcome in collaboration with our statistician. For imaging, multiple, non-overlapping regions of interest (ROI will be drawn over the tumor for each of four 10 mm slices (4 cm of volume) and blood perfusion values will be obtained. Descriptive statistics will be provided for all outcome measurements and goodness of fit tests (e.g. Chi-square, Kolmogorov Smirnov) will be conducted to assess the distribution of the changes in functional imaging. As appropriate, we will use parametric (t-test) or nonparametric (Wilcoxon Rank-Sum) tests to compare between the two groups of patients stratified by response and PFS status. To test the prognostic effect of changes in these parameters on OS and PFS, we will utilize the Cox proportional hazards model. In addition, comparison to RECIST based measurement, tumor volume and tumor density will be performed by using well established protocols in our department to evaluate the most sensitive image biomarker of monitoring response and predicting clinical outcome.

12.1.2.4 Tolerability and safety analysis
Preliminary Phase I data revealed excellent tolerability. For the safety analysis, all enrolled patients who receive at least one dose of cabozantinib will have information collected on adverse events, which will be summarized by dose, severity as assessed by the Common Toxicity Criteria for Adverse Events (CTCAE), v. 4.0 and relationship to Study Drug.

12.2 Rationale for Sample Size

The data from recent phase II clinical trials of agents targeting the VEGF or mTOR pathways has guided our trial design and sample size calculation. The Phase II trial of the VEGF inhibitor, bevacizumab in patients with carcinoid tumors revealed a response rate of 18% [4]. A Phase II trial of the mTOR inhibitor, everolimus in patients with low grade neuroendocrine tumors demonstrated response rates of 20% [37]. Similarly, a phase II trial of sunitinib performed in neuroendocrine tumors demonstrated a response rate of 16.7% in pancreatic neuroendocrine tumors and 2.4% in patients with carcinoid tumors [3]. More recently, Phase III trials of both sunitinib and everolimus have been published in patients with pancreatic neuroendocrine tumors, demonstrating lower overall response rates of 5% for everolimus (2% with placebo) and 9.3% for sunitinib (0% for placebo) [38, 39]. Notably, despite the low response rate observed with these targeted agents to date, 64% of patients receiving everolimus (versus 21% in placebo), and a large, but unreported percentage of patients receiving sunitinib demonstrated tumor shrinkage that did not meet partial response criteria.

Patients will be stratified depending upon whether they have a pancreatic neuroendocrine tumor or carcinoid tumor. For both subgroups, we hypothesize that cabozantinib will have a true response rate of greater than or equal to 12%, while the null hypothesize posits that the response rate will be ≤2%. The 12% response rate was selected on the basis of the response rate in the recent Phase III sunitinib trial in pancreatic neuroendocrine tumors, as well as the experience with multiple targeted agents in several phase II trials in patients with carcinoid tumors and pancreatic neuroendocrine tumors. A sample size of 35 achieves >80% power to detect a difference of 10% using a one-sided binomial test, with type I error of 3% and the population proportion under the null hypothesis is 2%. Therefore, 3 or more responders would be necessary to reject the null hypothesis. For efficacy evaluation of the study, all treated patients will be included when calculating the response rate. Therefore the overall sample size is anticipated to

be approximately 35 subjects for each tumor type, or 70 patients in total. Study patients will continue to be followed until progression or death, allowing us to capture all patients for this analysis.

Given the data above demonstrating tumor shrinkage and PFS benefit in patients treated with sunitinib or everolimus without impressive overall response rates, an overall response rate of 2%-12% would still be consistent with cabozantinib having activity in neuroendocrine tumors. As such, progression-free survival will be examined as one of the secondary endpoints, and we have not included a two-phase design in this protocol.

12.3 Reporting and Exclusions

12.3.1 Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Participants not completing 2 cycles of therapy due to reasons unrelated to study drugs will not be evaluated for DLT, but will be replaced.

12.3.2 Evaluation of response

All participants included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations. Each participant 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). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

13. PUBLICATION PLAN

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

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15. APPENDICES

Appendix A - Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	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 – Cabozantinib Tablets

Investigational Treatment: Cabozantinib tablets

Chemical Name: *N*--*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Exelixis internal number: XL184

Exelixis will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 100 mg and 20 mg yellow film coated tablets. 100 mg tablets are caplet-shaped, and the 20 mg tablets are round. The components of the tablets are listed in Table 1.

Table 1: Cabozantinib Tablet Components and Composition

Ingredient	**Function**	**% w/w**
XL-184 Drug Substance (25% drug load as free base)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00