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A PHASE II STUDY TO EVALUATE THE EFFECTS OF CABOZANTINIB IN PATIENTS WITH UNRESECTABLE/METASTATIC ADRENOCORTICAL CARCINOMA

PROTOCOL NUMBER:2016-0741

STUDY DRUG: Cabozantinib (XL184)

SPONSOR: THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

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AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
BP	blood pressure
BUN	blood urea nitrogen
CHF	congestive heart failure
CrCl	creatinine clearance
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESC	Exelixis Safety Committee
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
ICH	International Conference on Harmonisation
IME	important medical event
INR	International Normalized Ratio
IRB	Institutional Review Board
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LMWH	low molecular weight heparin
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCI	National Cancer Institute

NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PD	progressive disease
PE	pulmonary embolism
PI	principal investigator
PPE	palmar-plantar erythrodysesthesia
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
ONJ	osteonecrosis of the jaw
QTc	corrected QT interval
QTcF	QTc calculated by the Friderica formula
RBC	red blood cell
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SBP	systolic blood pressure
TFT	thyroid function test
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein/urine creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)

1 BACKGROUND AND RATIONALE

1.1 Background

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis and limited response to therapy (1-3). Recurrence after surgical resection is very common in patients presenting with localized disease and systemic therapy is the primary treatment for patients with recurrent or advanced disease. The combination of cisplatin/etoposide/doxorubicin/mitotane is the current standard of care for metastatic ACC. This combination has a suboptimal response rate of 23% with median time to progression of about 5 months while second line therapy (streptozocin with mitotane) has response rate of 9% with median time to progression of about 2 months (4).

In order to understand factors related to chemotherapy resistance and to identify better treatment options, we recently studied the role of hepatocyte growth factor (HGF) and its receptor (cMET) in ACC. Transcriptomic and immunohistochemical analyses indicated that increased HGF/cMET expression in human ACC samples was positively associated with cancer-related biologic processes, including proliferation and angiogenesis, and negatively correlated with apoptosis. Accordingly, treatment of ACC cells with exogenous HGF resulted in increased cell proliferation in vitro and in vivo while short hairpin RNA-mediated knockdown or pharmacologic inhibition of cMET with cabozantinib suppressed cell proliferation and tumor growth (Figure 1)(5).

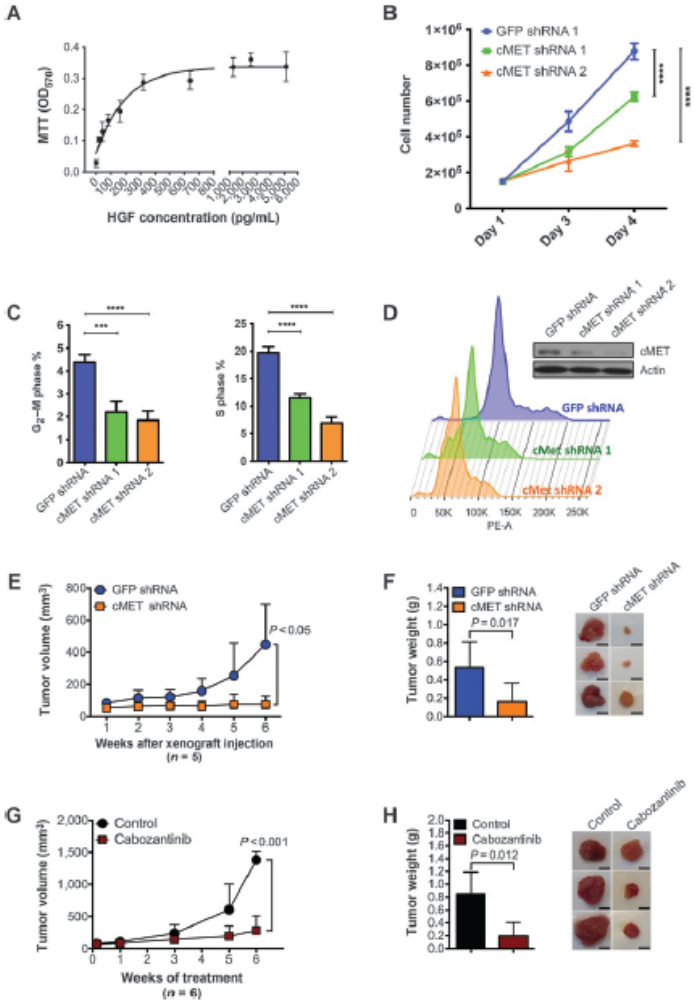

Figure 1: Increased HGF/cMET signaling is associated with enhanced proliferation, tumor growth, and reduced apoptosis in adrenocortical carcinoma .A, cell viability measured by MTT assay ofNCI-H295R cells cultured at different concentrations of recombinant human HGF for 7 days. B, knockdown of MET expression by lentiviral shRNAs decreases adrenocortical carcinoma cell proliferation. C, knockdown of MET expression by lentiviral shRNAs decreases percentages of adrenocortical carcinoma cells in G2–M or S-phase. D, cell-cycle progression analysis showing the important role of cMET in adrenocortical carcinoma cell proliferation. E, mean tumor volume in mice at different weeks after xenografting of H295R–GFP–shRNA or H295R-cMET-shRNA cells (5 mice per group). F, mean tumor weights in mice 6 weeks after xenografting of H295R-GFP-shRNA or H295R-cMET-shRNA cells (5 mice per group; left) and representative images of xenografted tumors harvested from the mice (right; scale bars, 5mm). G, mean volumes of tumors formed from xenografted H295R cells at different weeks after treatment of randomized control and cabozantinib treated mice (6mice per group). H, mean weights of tumors from randomized control and cabozantinib-treated mice after 6 weeks of treatment (6 mice per group; left) and representative images of xenografted tumors harvested from the mice (right; scale bars, 5 mm). Statistical significance of data in F and H was calculated by one-way ANOVA (Reference Phan L et al. Cancer Research 2015).

Moreover, exposure of ACC cell line to commonly used treatments in ACC (mitotane, cisplatin, or radiation) rapidly induced pro-cMET expression and was associated with an enrichment of genes (e.g., CYP450 family) related to therapy resistance, further implicating cMET in the anticancer drug response. Together, these data suggest an important role for HGF/cMET signaling in adrenocortical carcinoma growth and resistance to commonly used treatments (5). Targeting cMET, alone or in combination with other drugs, could provide a breakthrough in the management of this aggressive cancer.

Based on these preclinical data, we have recently used cabozantinib outside clinical trial to treat a patient with progressive ACC that failed multiple lines of treatment (Figure 2A). Within 4 weeks of cabozantinib use, target lesions stopped growing and slightly reduced in size (one target lesion in left upper quadrant reduced from 8.3 cm in greatest dimension at baseline to 7 cm and second target lesion in the upper pole of the right kidney reduced from 7.3 cm in greatest dimension to 6.6 cm)(Figure 2B). This patient had grade 1 fatigue and mucositis and continued to have very good performance status (ECOG 1) while on cabozantinib 60 mg daily. Cabozantinib was maintained and radiological stability was demonstrated stable disease for 12 months on therapy.

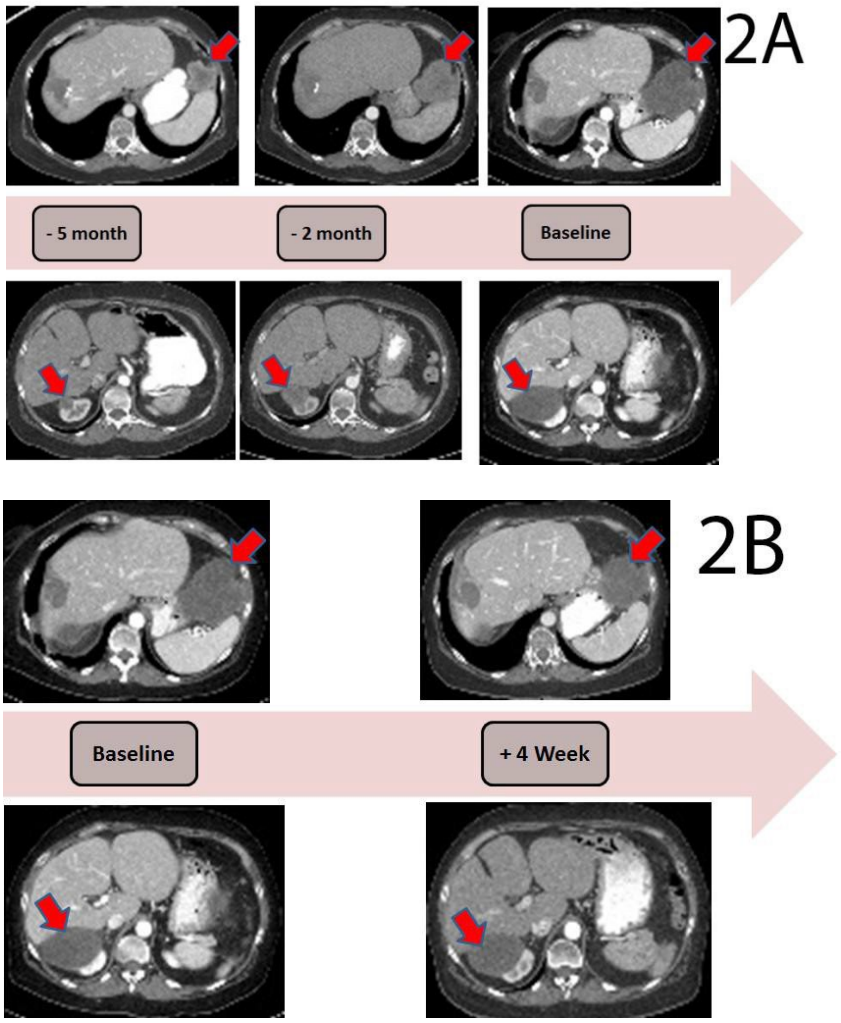

Figure 2: A. ACC progression prior to cabozantinib use (upper panel target lesion in left upper quadrant and lower panel target lesion 2 in upper pole of right kidney). B. response of target lesions to cabozantinib 60 mg daily. *The response was preserved at 12 months on treatment*

Hypothesis

cMET activation is correlated with cancer hallmarks in ACC and appears to be an important mechanism in resistance to therapy. cMET and VEGFRs cooperate to promote tumor angiogenesis and cMET up-regulation may occur as a response to the VEGFs pathway inhibition leading to tumor resistance and growth(6).

Cabozantinib is a tyrosine kinase inhibitor with antiangiogenic and antitumor activity that targets the VEGF, c-MET, and RET receptors. Cabozantinib drug is approved for the treatment of medullary thyroid carcinoma and was recently approved in renal cell carcinoma (7, 8). Receptor tyrosine kinases (RTKs) regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair (12). Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers. The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) (12). c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (e.g., renal tubular cells, gland formation, etc.), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Up-regulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells in vitro and metastases in vivo (see latest version of the Investigator's Brochure). C-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorgenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (e.g., NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination in vivo (12). A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity (13), either by means of c-Met kinase overexpression (14), or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF . These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis (15).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability(16). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (17) . High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (i.e., therapy-resistant) breast cancer. The expression of VEGF and VEGFR-2 as well as microvessel density were higher in ACC compared to benign adrenal neoplasms (18). Despite of this, targeting VEGF signaling alone had limited clinical efficacy in ACC (19). Therefore, simultaneous inhibition of cMET and VEGFRs by cabozantinib provides a broad spectrum of antineoplastic activity and its use in ACC is appealing based on recently published preclinical data and early reports of human experience.

As an exploratory objective, we also aim to generate crucial preliminary data about the changes in immune markers in association with cabozantinib study. The adrenal gland can be recognized by the immune system and develop autoimmune adrenalitis and adrenal insufficiency (Addison's disease).

Mononuclear cells infiltrating (mainly CD3+) the adrenal glands on autopsies are more common in people 60 years and older (63%) compared to subjects <49 years old (7%). CD4+ cells are more common than CD8+ cells and are thought to have been activated by interleukin 2 receptor(20). In Merkel cell carcinoma, higher CD3+ and CD8+ immune infiltrates at the periphery of tumor were associated with improved overall survival (21). Tyrosine kinase inhibitors are increasingly used in multiple malignancies. Imatinib mesylate has known clinical benefits in gastrointestinal stromal tumors (GIST) and has been reported to have direct effects on tumor cells as well as indirect immunostimulatory effects on lymphocytes and high densities of CD3+ tumor infiltrating cells correlated with PFS (22). The number of infiltrating FoxP3(+) regulatory T cells and macrophages is even higher in in metastatic GIST compared to primary lesions. Imatinib and sunitinib increased the secretion of anti-inflammatory IL-10 in macrophage cultures thus affecting the tumor microenvironment (23). Similarly, cabozantinib has direct effect on tumor cells as well as immunomodulatory effect that enhances the sensitivity of tumor cells to T cell-mediated lysis (24). Clinical trials using immunotherapy in ACC are emerging and it remains unclear if prior use of immunotherapy will affect the response to TKIs in ACC or if using TKIs can enhance the response to subsequent immunotherapy. Thus, data generated from patients in this study can further our understanding of the complex effect of TKIs on tumor immune infiltrate and could lead to new treatment combinations in the future.

Analyses of tumor and blood samples: These studies will be performed at MDACC in collaboration with Dr. Ignacio Wistuba who is supervising the Translational Molecular Pathology - Immunoprofiling Laboratory (TMP-IL). Patient samples will be collected to perform immunologic analyses. The study will allow for the collection of blood samples to be drawn at the time of routine blood-draw to assess circulating immune markers. Whole blood, plasma, serum, peripheral blood mononuclear cells (PBMCs) and other secreted markers (such as cytokines) may be collected at 3 time points (before and during treatment and at time of disease progression) and processed at the TMP-IL for further downstream analyses.

Optional biopsies will be used for immune-profiling analysis (core needle biopsies (CNBs). Fresh tissue samples will be sent immediately after collection to TMP-IL. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected, including 2 for clinical processing and 3 additional passes will be attempted to obtain the research core samples.

Cores 1 and 2: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples)

Cores 3-4: Flash freezing in liquid nitrogen.

Core 5: Flow cytometry analysis of TIL and TME on fresh tissue.

All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells to confirm the presence of tumor cells, as well as their abundance (tumor cellularity); b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available for review.

Using immunohistochemistry (IHC) and multiplex immunofluorescence (IF) approach that is available in the TMP-IL (Drs. Wistuba and Jaime Rodriguez Canales), we will quantitatively assess multiple immune markers. Fresh frozen tissues will be also used for analysis of immune markers. IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All

pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using the Vectra Inform™ (Perkin-Elmer) software. Nucleic acids (DNA and RNA) and protein extraction: Blood (plasma and PMBCs) and tumor (CNB) samples will be subjected to extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.

High order flow cytometry panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells and their respective receptors such as PD-L1 on infiltrating myeloid cells or tumor. Briefly, 50 cc of heparinized peripheral blood from cancer patients prior to the initiation of treatment, during treatment, and at time of progression will be processed fresh (within 24h of being drawn) for PBMC isolation by ITB. PBMCs will be cryopreserved and stored in Liquid Nitrogen until use. Flow cytometric analysis will be conducted retrospectively on cryopreserved PBMCs. When appropriate, cells will be thawed and stained immediately. All time points belonging to a patient will be stained and acquired at the same time to avoid any technical variation (sample at time of progression will be omitted for responders if analysis needs to be completed when patient is still responding). We expect that half of the study participants will agree to have the optional biopsies and we anticipate to collect blood samples from all participants.

In another exploratory objective, we will attempt to assess the role of genetic variants of drug disposition genes on the PK of cabozantinib.For the past decades, pharmacogenomic association studies have revealed a significant influence of genetic variants on the disposition of various drugs prescribed in the cancer care setting (e.g. tacrolimus, irinotecan, 5-fluorouracil and 6-MP). This continues to be an increasingly popular area of pharmacological research. Cabozantinib is a substrate for both cytochrome P450 3A4 (CYP3A4) and the drug transporter MRP2, and maybe a substrate for other obscure drug metabolizing enzymes and transporters. Hypothetically, single nucleotide polymorphisms (SNPs) in these genes may affect cabozantinib PK. However, there is a dearth of data regarding these potential genetic associations. To preliminary assess for potential associations, a single blood sample (~ 10 ml) will be collected at the patient's first clinic visit for exploratory pharmacogenomic testing. Whole blood will be collected into pre-labelled lavender-top collection tubes. Genomic DNA will be isolated from each blood sample using the GenElute Blood Genomic DNA Kit (Sigma-Aldrich Co), or similar DNA extraction kit, in the Pharmaceutics Research Laboratory (Division of Pharmacy, Department of Pharmacy Research) by trained research staff. Isolated DNA will be transferred to pre-labelled, de-identified cryovials and frozen at -80ºC in the Pharmacy Research Laboratory freezer prior to shipment. DNA samples will be shipped by research staff in the Pharmacy Research Laboratory to an external laboratory (Avera Institute for Human Genetics, Sioux Falls, SD) for analysis of over 2,000 polymorphisms in drug disposition genes using the powerful DMET™ Plus Array (Affymetrix). Preliminary pharmacogenomic data will be a crucial step towards further understanding the disposition of cabozantinib in cancer patients.

1.2 Cabozantinib (XL184)

1.2.1 Pharmacology

Full details can be found in the latest version of the Investigator's Brochure. Cabozantinib is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and

angiogenesis (see latest version of the Investigator's Brochure). The primary targets of cabozantinib are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and in vivo pharmacodynamic activity of cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

1.2.2 Cabozantinib Nonclinical Toxicology

Full details can be found in the latest version of the Investigator's Brochure. The carcinogenic potential of cabozantinib is being evaluated in an ongoing two-year bioassay in rats. No carcinogenic signal was observed in the rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks.

1.2.3 Clinical Experience

Cabozantinib has two FDA approved indications. First FDA approval for cabozantinib (Cometriq) was on November 29, 2012 to treat medullary thyroid carcinoma and on 21 March 2014, it was approved by the European Commission for the treatment of adult subjects with progressive, unresectable locally advanced or metastatic MTC. Recently cabozantinib (Cabometyx) was FDA approved and on April 25, 2016 for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy.

A summary of 15 clinical studies of cabozantinib for oncology is included in the latest version of theInvestigator's Brochure). In addition, there are eleven clinical pharmacology studies; nine were conducted in healthy subjects alone, one study was conducted that included healthy subjects and subjects with renal impairment, and one study was conducted that included healthy subjects and subjects with hepatic impairment. In addition to these company-sponsored clinical studies, twenty-six investigator-sponsored trials (ISTs) and thirteen National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) trials have enrolled subjects in oncology indications.

1.2.3.1 Clinical Summary

Details of all studies may be found in the latest version of the Investigator's Brochure.

1.2.3.2 Clinical Safety Profile

A pooled analysis through 29 February 2016 included 2410 subjects with cancer who had been treated with single-agent cabozantinib in company-sponsored clinical trials. The subjects in that dataset were predominately White (83.4%) and male (77.5%) with a median age of 64.0 years. For ongoing studies, serious adverse event (SAE) data are summarized in the latest version of the Investigator's Brochure.

1.2.3.2.1 Adverse Events

The severity of AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) versions 3.0 and 4.0, and AE and SAE PTs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 for all studies. For AEs and SAEs, multiple occurrences of the same event in any individual subject are counted once at the highest grade reported. Events that were assessed as possibly related or probably related to cabozantinib are reported as "related," and events that were assessed as not related or unlikely related to cabozantinib are reported as "not related." In 2410 subjects treated with single-agent cabozantinib, AEs seen in ≥ 10% of subjects are summarized in the latest version of the Investigational Brochure. 2404 (99.8%) subjects had at least one AE while drug related AEs happened in 2324 (96.4%) subjects. 1512 subjects(62.7%) had ≥ grade 3 AEs. Most common drug related AEs include diarrhea 1300 (53.4%), fatigue 1281 (53.2%), nausea 1062(44.1%), decreased appetite 1080 (44.8%), vomiting 612(25.4%), weight loss 671 (27.8%), palmar-plantar erythrodysaesthesia syndrome 819(34%), constipation 345(14.3%), hypertension 603(25%), dysgeusia

605(25.1%), dysphonia 520(21.6%), asthenia 434(18%), dyspnea (187(7.8%), anemia 217(9%), stomatitis446(18.5%), abdominal pain 232(9.6%),aspartate aminotransferase increase 382(15.9%), back pain 56(2.3%), mucosal inflammation 423(17.6%), pain in extremity 180 (7.5%), headache 149(6.2%), alanine aminotransferase elevation 343 (14.2%), rash 300(12.4%), hypothyroidism 301(12.5%), cough 84(3.5%), peripheral edema 101(4.2%), dizziness 154(6.4%), arthralgia 76(3.2%), dyspepsia 224(9.3%), hypokalemia 136(5.6%), dry mouth 231 (9.6%), urinary tract infection 31(1.3%), dry skin 219(9.1%), hypomagnesemia 170(7.1%), dehydration 139(5.8%), muscle spasms 147(6.1%), hair color change 243(10.1%), pyrexia 44(1.8%), and insomnia 82(3.4%).

1.2.3.2.2 Serious Adverse Events

In 2410 subjects, drug related serious adverse events experienced by 602 subjects (25%) treated with single-agent cabozantinib excluding events of disease progression. This included 516 subjects (21.4%) who had ≥ grade 3 SAE.
These drug related SAEs are summarized in the latest version of the Investigational Brochure and included pulmonary embolism in 85 patients (3.5%), vomiting 40 patients(1.7%), nausea 47 patients(2%), dehydration 41 (1.7%), general health deterioration 13(0.5%), pneumonia 5(0.2%), anemia 17(0.7%), abdominal pain 13(0.5%), diarrhea 42(1.7%), deep vein thrombosis 21(0.9%), fatigue 27(1.1%), asthenia 20(0.8%), back pain 1, dyspnea 7(0.3%), pyrexia 5(0.2%), urinary tract infection 4(0.2%), acute renal failure 7(0.3%), convulsion 5(0.2%), hyponatremia 15(0.6%), decreased appetite 19(0.8%), sepsis 5(0.2%), bone pain 0, metastatic pain 1, pleural effusion 7(0.3%), and confusion 7(0.3%).

1.2.3.2.3 Deaths

In cancer subjects treated with single agent cabozantinib, death was reported in 10 out of 2410 subjects (0.4%) including death related to AEs in 3 (0.1%). Sudden death was seen in 2 patients (0.1%). [(see latest version of the Investigator's Brochure)].

1.2.3.3 Clinical Pharmacokinetics

Cabozantinib pharmacokinetics as single agent in clinical studies are summarized in [(see latest version of the Investigator's Brochure)].

Population PK analysis of cabozantinib was performed using data collected from 289 cabozantinib-treated subjects from XL184-301, XL184-001, and XL184-201 with solid tumors including MTC following oral administration of 140 mg daily doses. The predicted effective half-life is approximately 55 hours, V/F is approximately 349 L, and CL/F at steady-state is estimated to be 4.4 L/h. The terminal half-life (for predicting drug washout) is approximately 120 hours. Following oral administration of cabozantinib, Tmax ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared with a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%) (see latest version of the Investigator Brochure).
The PK evaluation of cabozantinib in the pediatric population is ongoing. A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib PK was not affected by age (20-86 years).
Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Results from a PK study of cabozantinib in subjects with renal impairment indicated that the ratios of geometric least squares (LS) mean for maximum plasma concentration (Cmax) and AUCs

(AUC0-t and AUC0-inf) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. For subjects with moderate renal impairment, both Cmax and AUCs appeared to be similar when compared to subjects with normal renal function (differences: < 3% and < 7%, respectively). Results from a PK evaluation of cabozantinib in subjects with hepatic impairment indicated that exposure (AUC0-inf) of cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment, respectively.
A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140-mg oral cabozantinib dose.
Cabozantinib is a substrate of cytochrome P450 (CYP3A4) in vitro. Inhibition of CYP3A4 reduced the formation of the cabozantinib N-oxide metabolite by > 80%.

Cabozantinib is a substrate of CYP3A4 *in vitro*. Inhibition of CYP3A4 *in vitro* reduced the formation of the cabozantinib N-oxide metabolite by > 80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (ie, a < 20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. In healthy volunteers, cabozantinib AUC was increased 38% with co-administration of the strong CYP3A4 inhibitor ketoconazole (XL184-007) and decreased 77% with co-administration of the strong CYP3A4 inducer rifampin (XL184-006).

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Ki_{app} = 4.6 µM), a mixed-type inhibitor of both CYP2C9 (Ki_{app} = 10.4 µM) and CYP2C19 (Ki_{app} = 28.8 µM), and a weak competitive inhibitor of CYP3A4 (estimated Ki_{app} = 282 µM) in human liver microsome (HLM) preparations. The IC_{50} value was 10.1 µM for CYP2B6 and IC_{50} values were > 20 µM for CYP1A2, CYP2D6, and CYP3A4 isozymes. Cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily dosing for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in subjects with solid tumors (XL184-008). Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers (XL184-018).
Cabozantinib is an inhibitor (IC_{50} = 7.0 µM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (eg, cyclosporine, delaviridine, efavirenz, emtricitabine) should be approached with caution, and subjects taking MRP2 inhibitors should be monitored for AEs.

Of interest, There was a differences in PK parameters from the two PopPK analyses (RCC patients and MTC patients) and appears to be result of higher clearance in MTC subjects, but the reason for this is not known (see latest version of the Investigator Brochure).

1.2.3.4 Clinical Activity

In phase 3 clinical trial in subjects with progressive MTC (214 on cabozantinib vs. 109 placebo), the estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (HR 0.28; 95% CI, 0.19 to 0.40; p < .001). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and RET mutation status (hereditary or sporadic). The final analysis of the secondary endpoint of OS included 218 events (217 were required) and showed a trend for increased

survival in the cabozantinib arm. The estimated median OS for the cabozantinib arm was 26.6 months versus 21.1 months for the placebo arm (HR = 0.85; 95% CI 0.64, 1.12; p = 0.2409).

In phase 3 trial of 119 subjects with advanced castrate resistant prostate carcinoma with bone metastases, the enrollment was stopped before the planned study population size of 246; a total of 119 subjects were enrolled. The primary analysis for the ITT population (n=119) did not demonstrate an improvement in the proportion of subjects with a pain response at Week 6 confirmed at Week 12 the cabozantinib arm compared with the mitoxantrone plus prednisone arm; the proportions of subjects experiencing a confirmed pain response were 15% and 17% for the two arms, respectively.
The secondary endpoints were BSR per IRF and OS. BSR was defined as a ≥ 30% decrease in total bone-scan lesion area compared with baseline without soft-tissue disease progression. The analysis of BSR per IRF at Week 12 without progression in soft tissue per mRECIST 1.1 demonstrated a greater improvement in the cabozantinib arm (31%; 95% CI: 20%, 43%) compared with the mitoxantrone plus prednisone arm (5%; 95% CI: 0%, 11%). In the analysis of OS that included 78 deaths out of the 196 pre-specified deaths, the stratified HR was 0.70 (95% CI: 0.44, 1.10).
In phase 3 study in renal cell carcinoma, 658 patients were randomized to either everolimus or cabozantinib. Median PFS was 7.4 months with cabozantinib and 3.8 months with everolimus with median duration of treatment of 7.6 months with cabozantinib and 4.4 months with everolimus. Dose reductions were needed in 60% of subjects treated with cabozantinib and the median average daily dose was 44 mg of cabozantinib. The rate of treatment discontinuation due to adverse events not related to renal-cell carcinoma was 9% in the cabozantinib group.

1.2.3.5 Translational Medicine

Details can be found in the latest version of the Investigator's Brochure.

1.3 Rationale

1.3.1 Rationale for the Study, Dose, and Schedule

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis and limited response to therapy (1-3). Recurrence after surgical resection is very common in patients presenting with localized disease and systemic therapy is the primary treatment for patients with recurrent or advanced disease. The combination of cisplatin/etoposide/doxorubicin/mitotane is the current standard of care for metastatic ACC. This combination has a suboptimal response rate of 23% with median time to progression of about 5 months while second line therapy (streptozocin with mitotane) has response rate of 9% with median time to progression of about 2 months (4).

In order to understand factors related to chemotherapy resistance and to identify better treatment options, we recently studied the role of hepatocyte growth factor (HGF) and its receptor (cMET) in ACC. Transcriptomic and immunohistochemical analyses indicated that increased HGF/cMET expression in human ACC samples was positively associated with cancer-related biologic processes, including proliferation and angiogenesis, and negatively correlated with apoptosis. Accordingly, treatment of ACC cells with exogenous HGF resulted in increased cell proliferation in vitro and in vivo while short hairpin RNA-mediated knockdown or pharmacologic inhibition of cMET with cabozantinib suppressed cell proliferation and tumor growth (Figure 1)(5). Moreover, exposure of ACC cell line to commonly used treatments in ACC (mitotane, cisplatin, or radiation) rapidly induced pro-cMET expression and was associated with an enrichment of genes (e.g., CYP450 family) related to therapy resistance, further implicating cMET in the anticancer drug response. Together, these data suggest an important role for HGF/cMET signaling in adrenocortical carcinoma growth and resistance to commonly used treatments (5). Targeting cMET, alone or in combination with other drugs, could provide a breakthrough in the management of this aggressive cancer.

Based on these preclinical data, we have recently used cabozantinib outside clinical trial to treat a patient with progressive ACC that failed multiple lines of treatment (Figure 2A). Within 4 weeks of

cabozantinib use, target lesions stopped growing and slightly reduced in size (one target lesion in left upper quadrant reduced from 8.3 cm in greatest dimension at baseline to 7 cm and second target lesion in the upper pole of the right kidney reduced from 7.3 cm in greatest dimension to 6.6 cm)(Figure 2B). This patient had grade 1 fatigue and mucositis and continued to have very good performance status (ECOG 1) while on cabozantinib 60 mg daily. Cabozantinb was maintained and radiological stability was demonstrated for 12 months on therapy.

Hypothesis

cMET activation is correlated with cancer hallmarks in ACC and appears to be an important mechanism in resistance to therapy. cMET and VEGFRs cooperate to promote tumor angiogenesis and cMET up-regulation may occur as a response to the VEGFs pathway inhibition leading to tumor resistance and growth(6).

Cabozantinib is a tyrosine kinase inhibitor with antiangiogenic and antitumor activity that targets the VEGF, c-MET, and RET receptors. This drug was approved for the treatment of medullary thyroid carcinoma and recently approved in renal cell carcinoma (7, 8). Therefore, simultaneous inhibition of cMET and VEGFRs by cabozantinib provides a broad spectrum of antineoplastic activity and its use in ACC is appealing based on recently published preclinical data and preliminary human experience.

We also hypothesize that cabozantinib use has immunomodulatory effect on ACC that can include a change in tumor infiltrating lymphocytes profile. The optional biopsies from few patients has the potential of furthering our understanding about the effect of cabozantinib on tumor immunity and could open the door for combination therapy in the future.

The study plan is to use cabozantinib with initiation dose is 60 mg daily by mouth. The dose can be reduced to 40 mg then 20 mg a day based on tolerability and adverse effects. Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. Considering the possibility mitotane induction of CYP3A4 that can reduce cabozantinib levels, subjects who used mitotane within 6 months of study participation will have PK levels (obtained on day 1 and day 29+/- 5 days) analyzed after collection to allow increasing cabozantinib dose to 80 mg a day if AUC for plasma cabozantinib was < 50% of expected AUC. Further dose titration in these subjects to 60 mg, 40 mg and 20 mg will be done based on tolerability and adverse effects. In the remaining study subjects (estimated 12 out of 18 patients), samples will be analyzed a-posteriori after completing study enrollment.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The objectives of this study are as follows:

Primary objective: To estimate progression free survival at 4 months

Secondary objectives:

1. Best overall response rate
2. Overall survival (O.S)
3. Toxicity assessment by the Common Terminology Criteria for Adverse Events (CTCAE) V4.0

Exploratory objectives:

1. Pharmacokinetics of cabozantinib plasma levels to assess correlation with response to therapy
2. Steroid hormone biomarkers as markers of disease response.
3. Study the effect of cabozantinib on immune markers by obtaining optional biopsy and blood samples collection at baseline, during therapy and at time of progression.
4. Pharmacogenomics of drug disposition gene variants that potentially influence cabozantinib PK.

2.2 Study Design

2.2.1 Overview of Study Design

This is an open label Phase II clinical trial using cabozantinib in patients with unresectable/advanced ACC.

2.3 Blinding and randomization

N/A

2.4 Study Sites

This study will be conducted The University of Texas MD Anderson IND Office

2.5 Withdrawals

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

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Sections 3.3.2 and 3.3.2.1;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g, male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator / MD Anderson IND Office;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- The minimum dose of study treatment will be 20 mg once daily (qd). Subjects who cannot tolerate 20 mg qd will have study treatment discontinued;

- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

2.5.1 Replacements

NA

3 TREATMENTS

3.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

3.1.1 Investigational Treatment

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

3.1.2 Cabozantinib Tablets

Exelixis internal number: XL184

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round and the 60 mg tablets are oval. The components of the tablets are listed in Table 3-1.

Table 3-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disinegrant	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

3.2 Dose, Schedule and Route

Subjects will receive cabozantinib orally at a (starting) dose of 60 mg once daily, on a continuous basis.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 3.3 below.

3.3 Cabozantinib Dose Modifications, Interruptions, and Discontinuation

Subjects will be monitored for AEs from the time of from the time of first study intervention through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.

- Dose modification criteria for cabozantinib are shown in Table 3-3. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.

- The assigned starting dose for cabozantinib is 60 mg/day. 2 dose reduction levels of cabozantinib are permitted (see Table 3-2).

- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 3-3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.

- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be 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 per the discretion of the investigator.

- Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

- Considering the possibility mitotane induction of CYP3A4 that can reduce cabozantinib levels, subjects who used mitotane within 6 months of study participation will have PK levels (obtained on day 1 and day 29+/- 5 days) analyzed after collection to allow increasing

cabozantinib dose to 80 mg a day if AUC for plasma cabozantinib was <50% of expected AUC provided AE levels are ≤ grade 1. Further dose titration in these subjects to 60 mg, 40 mg and 20 mg will be done based on tolerability and adverse effects. The remaining study participants will have their samples analyzed after completing study enrollment.

-

Guidelines for the management of specific AEs are provided in Section 3.3.2.

Table 3-2: Dose Reductions of Cabozantinib

Assigned dose	First Dose Level Reduction	Second Dose Level Reduction
60-mg cabozantinib oral qd	40-mg cabozantinib oral qd	20-mg cabozantinib oral qd

qd, once daily
Cabozantinib should be discontinued if a qd dose of 20-mg cabozantinib (minimum dose) is not tolerated

Table 3-3: Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.4.0 Grade	Recommended Guidelines for Management [a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Resume cabozantinib following recovery to Grade 1 (or baseline). Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator and agreed by the MD Anderson IND Office • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 3.3.2. For re-treatment criteria of study treatment after a dose hold see Section 3.3.1.1.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

3.3.1.1 Cabozantinib Dose Reinstitution and Reescalation

If the subject recovers from his or her toxicities to CTCAE v.4.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 3-2 for the schedule of dose reductions).

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 60 mg/day) may be allowed at the discretion of the investigator and agreement of the MD Anderson IND Office for AEs which have resolved or recovered to ≤ Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, and renal).

3.3.2 Warnings and Precautions and Guidelines for the Management of Adverse Events

The most frequent adverse events experienced by ≥ 20% of subjects treated with cabozantinib were diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, PPES, constipation, hypertension, dysgeusia, dysphonia, and asthenia.

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib include anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lipase increased, lactate dehydrogenase (LDH) increased, neutropenia, ALP increased, hyponatremia, and leukopenia. Mild to moderate QTc interval prolongation (10-15ms) has also been observed with a QT interval calculated by the Fridericia formula (QTcF) not exceeding 500 ms. Prolonged QTc appears to be a very rare event and no torsades de pointes have been reported (see latest version of the Investigator Brochure).

Subjects may also experience medically important but less frequent adverse events including arterial and venous thrombotic AEs (eg, DVT, pulmonary embolism [PE], transient ischemic attack [TIA], and myocardial infarction [MI]), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reverse posterior leukoencephalopathy syndrome (RPLS).

Cabozantinib treatment should be permanently discontinued for the following adverse events: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, malignant hypertension, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw (ONJ), and RPLS.

Guidelines for the management of AEs (i.e., dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable per Investigator judgment. All AEs should also be managed with supportive care at the earliest signs of toxicity. Adverse reactions are presumed to be attributable to study drug. Adverse events classified as “not related” are defined as AEs that are, without question, not associated with the study treatment and definitely attributable to another cause.

The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2 to 3 weeks to reach steady state. If AEs attributable to

cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, because without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.

Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting. In addition, earlier onset for events of dehydration was observed in subjects with CRPC when compared with subjects with other tumor types.

3.3.2.1 Guidelines for Management of Potential Adverse Events

Sections 3.3.2.2 – 3.3.2.19 present management guidelines or warnings/precautions for the following cabozantinib treatment-emergent adverse events/serious adverse events of particular interest

- Gastrointestinal disorders (diarrhea, nausea and vomiting , dehydration [prostate cancer studies], stomatitis and mucositis)
- Hepatobiliary disorders (elevated ALT and AST)
- Hematological disorders
- Fatigue, anorexia, and weight loss
- Skin disorders (palmar-plantar erythrodysesthesia syndrome [PPES] and rash)
- Wound healing and surgery
- Hypertension
- Thromboembolic events (venous and arterial)
- Proteinuria
- QTc prolongation
- Hypophosphatemia
- Thyroid function disorders
- Hemorrhagic events
- Osteonecrosis of the jaw (ONJ)
- Angioedema
- Musculoskeletal and connective tissue disorders
- Respiratory, thoracic, and mediastinal disorders

Please refer to the latest version of the Investigator's Brochure for additional practice guidelines and management recommendations for these and other AEs potentially related to cabozantinib treatment (e.g. intra-abdominal and pelvic abscess; nervous system disorders; infections and infestations; and respiratory thoracic and mediastinal disorders) use in specific populations, and overdose and first aid measures for accidental cabozantinib exposure.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely for all AEs. As with other agents in development, additional AEs are unknown.

3.3.2.2 Gastrointestinal Disorders

The most common non-hepatobiliary GI AEs reported in clinical studies with cabozantinib regardless of causality are diarrhea, nausea, decreased appetite, vomiting, constipation, stomatitis and abdominal pain.

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/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 3-3.

In addition, general supportive measures should be implemented including hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care in accordance to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure (see Sections 3.4.4). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. When therapy with antiemetic agents does not control the nausea or vomiting to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 3-3.Dehydration may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

Dehydration

Dehydration events have been identified with comparable incidence and occurring in a shorter time to onset in the prostate cancer studies than previously experienced with cabozantinib in other tumor types. Extra monitoring/medical management including electrolyte monitoring and/or early dose reduction of patients exhibiting dehydration symptoms and those with risk factors for dehydration is indicated.

Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for 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 nontraumatic cleansing and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered per Table 3-2 and Table 3-3.

3.3.2.3 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. 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 should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

Subjects on this study may enter with increased ALT/AST serum levels up to 3 × ULN. Dose reductions of study treatment should be considered in any subject who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A subject who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (see Table 3-2) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In subjects with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In subjects who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and cabozantinib treatment interrupted. Reinstitution of study treatment after recovery of ALT, AST, and bilirubin to Grade 1 or baseline level is at the discretion of the investigator.

3.3.2.4 Hematological Disorders

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.

Complete blood counts with differentials and platelets should be performed regularly. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. Results of such tests are to be forwarded to the local laboratory data management vendor.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.

3.3.2.5 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated in accordance to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see latest version of the Investigator's). Refer to Table 3-3 for general management guidelines.

Anorexia and weight loss should be managed in accordance to local standard of care including nutritional support. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced per Table 3-2 and Table 3-3.

3.3.2.6 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30, avoidance of exposure of hands and feet to hot water, removal of calluses, protection of pressure-sensitive areas of hands and feet, and use of thick cotton gloves and socks to prevent injury and to keep

the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study treatment are presented in Table 3-4.

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

Table 3-4: Management of Treatment-Emergent Hand-Foot Syndrome (PPES)

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

3.3.2.7 Wound Healing and Surgery

VEGFR 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 before starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. If possible, cabozantinib treatment should be stopped for at least 28 days prior to major surgery.

3.3.2.8 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported among subjects treated with cabozantinib.

Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 3-5. Blood pressure should be monitored in a constant position at each visit (either sitting or supine). In general, subjects with known hypertension should be optimally managed before study entry. Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes after 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 therapeutic action. It is recommended that this second visit occurs within 1-2 weeks.

Cabozantinib should be discontinued in subjects with hypertensive crises or hypertensive encephalopathy.

Table 3-5: Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce study treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt study treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, study treatment should be dose reduced further or interrupted • Study treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start study treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency [b]	• Discontinue study treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.

[b] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

3.3.2.9 Thromboembolic Events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued. See Section 3.4.4 for additional restrictions on anticoagulation therapy.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

3.3.2.10 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Management guidelines are provided in Table 3-6.

Cabozantinib should be permanently discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with hypoalbuminemia and peripheral edema [hyperlipidemia and thrombotic disease may also be present]) or any other relevant renal disease.

Table 3-6: Management of Treatment-emergent Proteinuria

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-hour protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 hours on 24-hour urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider holding cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose hold unless otherwise approved by MD Anderson IND Office. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue all study treatment

UPCR, urine protein/creatinine ratio.

3.3.2.11 Corrected QTc Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms.

Unless otherwise specified in certain protocols, only subjects with a baseline QTcF ≤ 500 msec are eligible for cabozantinib research studies. Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or drugs

known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Withhold study treatment
- Immediately notify the MD Anderson IND Office
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed according to protocol procedures
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

3.3.2.12 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Other causes of hypophosphatemia should be ruled out and/or these causes treated in accordance to standard of care. Mild to moderate hypophosphatemia

should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements in accordance to standard clinical practice guidelines.

Clinically relevant hypophosphatemia should be managed in accordance to the dose modification guidelines as outlined in Table 3-2 and Table 3-3 or as clinically indicated.

3.3.2.13 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib therapy and other tyrosine kinase inhibitors as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent. Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 3-2 and Table 3-3.

3.3.2.14 Hemorrhagic Events

Hemorrhagic events have been reported with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors before 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 of the lung with cavitary lesions or tumor lesions which invades or encases major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis;
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis;
- History of clinically significant hemoptysis.

The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Though the incidence of CNS hemorrhage events in a study of subjects with GB was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of hemorrhage in GB translates to a risk of hemorrhage for subjects with brain metastases. Currently, brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 5 mL of red blood).

3.3.2.15 GI Perforation/Fistula and Non-GI Fistula Formation

Gastrointestinal perforation/GI fistula: Prior to initiation of treatment with cabozantinib, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Tumors invading GI or respiratory tracts
- Active peptic ulcer disease, inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Ongoing visceral complications from prior radiation therapy
- Prior GI surgery (particularly when associated with delayed or incomplete healing)

Complete healing following abdominal surgery and/or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

After starting cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula are present.

Discontinue cabozantinib treatment in subjects who have been diagnosed with GI perforation/fistula.

Non-GI fistula formation: Complications from radiation therapy has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (ie, radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 3 months of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

Discontinue cabozantinib treatment in subjects who have been diagnosed with non-GI fistula.

3.3.2.16 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in subjects treated with cabozantinib. Additional risk factors for ONJ have been identified including the use of bisphosphonates and denosumab, chemotherapy, corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ.

Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib therapy. Advise subjects regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be held for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

3.3.2.17 Angioedema

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

3.3.2.18 Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and approved by the MD Anderson IND Office. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

3.3.2.19 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation (Section 03.3.2.15) and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

3.4 Concomitant Medications and Therapies

3.4.1 Anticancer Therapy

Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

3.4.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the medical record.

3.4.3 Allowed Therapies

- Antiemetics and antidiarrheal medications are allowed prophylactically in accordance to standard clinical practice if clinically indicated;

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);

- Drugs to control hormonal excess symptoms (spironolactone, metyrapone, mifepristone, and ketoconazole). If using strong CYP3A4 inhibitor such as ketoconazole is unavoidable, cabozantinib dose needs to be reduced by 20 mg. Resuming prior dose level can be done 2-3 days after discontinuing ketoconazole.

- Drugs used to control bone loss (e.g., bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require principal investigator's approval;

- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice;

  - Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
    - At the time of first dose of study treatment:
      - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
      - Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 3.4.4 for prohibited anticoagulants.
    - After first dose of study treatment:
      - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
      - Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. See section 3.3.2.9 for management of thromboembolic complications while on study. See section 3.4.4 for prohibited anticoagulants.
    - Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions,

monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used concomitantly with heparin or factor Xa inhibitors due to the increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines.

3.4.4 Prohibited or Restricted Therapies

The following therapies are prohibited while the subject is on study:

- Any investigational agent or investigational medical device;
- Any drug or herbal product used specifically for the treatment of ACC ;
- Oral anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardio-protection per local applicable guidelines), until 4 weeks after cabozantinib has been permanently discontinued.
- Any other systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides) and local anticancer treatment such as surgery, ablation, or embolization.

The following therapies should be avoided if possible, while the subject is on study:

- Palliative external radiation to bone metastasis for bone pain should not be routinely performed while on study but can be considered as a treatment for non-target lesions at the investigator's discretion.
- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence and/or progression associated with erythropoietin;
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided if possible. Selection

of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;

- 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, because this could significantly increase the exposure to cabozantinib;

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and is not permitted. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Ketoconazole use will be permitted to treat Cushing syndrome if clinically unavoidable. Cabozantinib dose needs to be reduced by 20 mg when using ketoconazole. Resuming prior dose level is permitted 2-3 days after discontinuing ketoconazole.

Additional information on potential drug interactions with cabozantinib is provided in Section 3.4.5.

3.4.5 Potential Drug Interactions

Cytochrome P450 (CYP): 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 area under the plasma drug concentration time curve (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 with CYP2C8 (i.e., CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, 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.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% 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 and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided 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.

In addition, cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) 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).

Other Interactions:

Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose of cabozantinib. After the 2-hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

Additional details regarding potential drug interactions with cabozantinib can be found in the latest version of the investigator brochure.

3.5 Compliance

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

3.6 Study Drug Accountability

The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled and destroyed in accordance with applicable state and federal regulations and in accordance to MD Anderson institutional policies and procedures for drug destruction.

4 STUDY POPULATION

4.1 Inclusion Criteria

A subject must fully meet all of the following criteria to be eligible for the study:

1. The subject is ≥ 18 years old on the day of consent
2. Histological confirmation of ACC based on either: i). Weiss Score of ≥ 3 in patients who had earlier surgical resection (Lin-*Weiss-Bisceglia system* will be used for oncocytic ACC) OR ii). biopsy results compatible with ACC in the context of clinical setting highly suggestive of ACC (adrenal mass > 4 cm invading surrounding organs or associated with distant metastases).
3. Locally advanced or metastatic disease not amenable to surgery with curative intent with measurable disease per RECIST 1.1 (9) as determined by the investigator based on an assessment of all known disease sites by computerized tomography (CT) scan or magnetic resonance imaging (MRI) of chest/abdomen/pelvis within 28 days before the first dose of cabozantinib. In patients with IV contrast allergy or borderline renal function, CT without IV contrast or 18 FDG PET CT may be used as clinically indicated
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
5. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy
6. Life expectancy of at least 3 months
7. Organ and marrow function and laboratory values as follows within 28 days prior to the first dose of cabozantinib:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 without colony stimulating factor support
    b. Platelets ≥ 100,000/mm^3
    c. Hemoglobin ≥ 9 g/dL
    d. Bilirubin ≤ 1.5 × the upper limit of normal (ULN). For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL
    e. Serum albumin ≥ 2.8 g/dl
    f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 50 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:
    Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72). Female: Multiply above result by 0.85
    g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × ULN
    h. No radiologic or clinical evidence of pancreatitis
    i. Urine protein/creatinine ratio (UPCR) ≤ 1
    j. Serum phosphorus ≥ 2.5mg/dl, cCalcium≥ 8mg/dL, magnesium≥ 1.2mg/dL, and potassium ≥ 3.0 meq/L (CTCAE V4.03 grade1 cut off levels).
8. Capable of understanding and complying with the protocol requirements and has signed the informed consent document.
9. Sexually active patients (men and women) must agree to use medically accepted barrier methods of contraception (e.g. male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All sexually active

subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s).

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

4.2 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

1. Received cytotoxic chemotherapy, radiation therapy, or targeted therapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies), or other investigational agent within 28 days of study enrollment.

2. For patients who received mitotane within 6 months of consenting, mitotane should have been stopped at least 28 days prior to study enrollment **AND** to have mitotane serum level of < 2 mg/L.

3. Prior treatment with cabozantinib or other cMET inhibitors

4. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment.

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

6. Prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 28 days before the first dose of study treatment.

7. Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:
   a. Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
   b. Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose

of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

8. Severe and uncontrolled Cushing syndrome despite medical management (e.g.: systolic blood pressure >160mmHg or hyperglycemia with fasting glucose above 300mg/dL)..

9. The use of strong CYP3A4 inhibitor (with the exception of ketoconazole).

10. The subject has experienced any of the following: a. clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment; b. hemoptysis≥ 0.5 teaspoon(2.5 mL) of red blood within 3 months before the first dose of study treatment; c. any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment. Tumor invading any major blood vessel at the time of study enrollment.

11. Evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib, or the subject with radiographic evidence of cavitating pulmonary lesion(s); or subjects with tumor invading or encasing any major blood vessels.

12. Uncontrolled, significant concurrent or recent illness including, but not limited to, the following conditions: *a. Cardiovascular disorders* including i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening ii. Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment iii. Any history of congenital long QT syndrome or iv. Any of the following within 6 months before the first dose of study treatment: • unstable angina pectoris • clinically-significant cardiac arrhythmias• stroke (including TIA, or other ischemic event) within 90 days of the first dose of study treatment • myocardial infarction • clinically significant thromboembolic event within 42 days of randomization requiring therapeutic anticoagulation. (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study) *b. Gastrointestinal disorders* particularly those associated with a high risk of perforation or fistula formation including: i. Any of the following within 28 days before the first dose of study treatment • intra-abdominal tumor/metastases invading GI mucosa • active peptic ulcer disease; patients must be completely recovered • inflammatory bowel disease (including ulcerative colitis and Crohn's disease), acute pancreatitis, pancreatic duct or common bile duct obstruction, acute diverticulitis, acute cholecystitis, symptomatic cholangitis or recent appendicitis within 1 month of first dose of cabozantinib; patients must be completely recovered from these conditions • clinically significant malabsorption syndrome, *c. Endocrine disorders,* uncontrolled Cushing syndrome despite of adequate medical therapy

13. Any of the following within 6 months before the first dose of study treatment: • abdominal fistula • gastrointestinal perforation •bowel obstruction or gastric outlet obstruction •intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 6 months before the first dose of study treatment. . •Other disorders associated with a high risk of fistula formation including PEG tube placement within 90 days before the first dose of study therapy

14. Other clinically significant disorders such as: i. active infection requiring systemic antibiotic treatment within 14 days before the first dose of study treatment ii. serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment iii. history of

organ transplant iv. Concurrent uncompensated hypothyroidism or thyroid dysfunction (TSH above 10) within 28 days before the first dose of study treatment v. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. Minor surgery within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

15. Unable to swallow tablets

16. A corrected QT interval calculated by the Fridericia formula (QTcF) >500 milliseconds within 28 days before first dose of study treatment.

17. Pregnant or breastfeeding.

18. A previously identified allergy or hypersensitivity to components of the study treatment formulation.

19. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

20. Evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment except for breast ductal carcinoma-in situ, cured non-melanoma skin cancer, or cured in situ cervical carcinoma

21. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality which, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Pre-Treatment Period

- During the Pre-Treatment Period, during which the participant will follow the schedule found in table 5-1, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. The following assessments will be conducted before subjects receiving their first dose of cabozantinib on this protocol:

1. For patients with measurable visceral metastases CT scans with contrast or MRI including chest/abdomen/and pelvis are required.
2. Demographics
3. Medical and cancer history/demographics
4. Height
5. Weight
6. Vital Signs
7. ECOG Performance Status

8. Clinical laboratory testing
    - chemistry panel (albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, , magnesium, phosphorus, potassium, sodium, total bilirubin, total protein)
    - hematology tests(CBC, differential, platelets)
    - adrenal hormonal assessment
    - urinalysis and UPCR
    - thyroid function tests (TSH, free T4)
    - pregnancy test (urine or serum) for women of child-bearing potential
    - PT/INR, PTT
    - Serum mitotane level if used mitotane within 6 months
9. ECGs
10. Physical examination, safety and adverse events evaluation will be performed at baseline.

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

5.2 Treatment Period

During the Treatment Period subjects will receive cabozantinib until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 2.5. Subjects should be instructed to immediately inform the principal investigator (PI) of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

The following schedule of assessments applies to all subjects (Table 5-1). More frequent assessments should be obtained if clinically indicated.

Table 5-1: Study Assessments

				Study Treatment Period			Post-Treatment Period
	Within 28 days before 1st Dose of Study Treatment	**Day 1**	**Day 1 of Weeks 3, 5, then every 4 weeks (± 5 days)**	**Day 1 of Week 5 (± 5 days)**	**Day 1 of Week 9 (± 5 days)**	**At Progression (+ 5 days)**	**30 - 37 Days after last dose**
Informed consent	X						
Demographics	X						
Medical and cancer history/demographics	X						
Physical examination	X		X				X
Height	X						
Weight	X		X				X
Vital signs	X		X				X
ECOG performance status	X		X				X
Clinical laboratory tests[1]	X		X[2]				X
Urinalysis and UPCR[10]	X		X[2]				X
PT/INR, PTT	X		X[12]				
TFTs (TSH, free T4)	X		X[2]				
12-lead ECG[8]	X		X				X
Cabozantinib administration		X	X (daily)				
Pregnancy test	X	X[9]	X[2]				X
Tumor assessment[3]	X		X (every 8 weeks)				
Adrenal hormonal profile[4]	X		X (every 8 weeks)				
Serum mitotane level[5]	X						
Concomitant medications	X	X	X				X
Adverse events	Continuous						X
Immunologic assessments[11]	X[11]				X[11]	X[11]	
Pharmacogenetic assessment[11]	X[11]						
Pharmacokinetic assessment[6]		X[6]		X[6]			
Optional biopsy[7]	X[7]			X[7]		X[7]	

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PT/INR, prothrombin time/International Normalized Ratio; PTT, partial prothrombin time, TFT, thyroid function test; UPCR, urine protein/urine creatinine ratio

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

[2]Every 8 weeks (+/-5 days) after the first 12 weeks

[3]All sites of known disease must be assessed with CT or MRI. In patients with IV contrast allergy or borderline renal function, CT without IV contrast or 18 FDG PET CT may be used as clinically indicated.

[4] No additional measurements of adrenal hormones (ACTH, cortisol, aldosterone, plasma renin activity, DHEA-sulfate, testosterone in women, estradiol in men and postmenopausal women)
are needed in patients with normal profile at baseline (Non-functioning ACC).

[5] No need for mitotane measurement in patients who have been off mitotane for > 6 months or never received mitotane.

[6]Full pharmacokinetic assessment on day 1 and day 29(+/- 5 days) then one trough level every 12 weeks (+/- 6 weeks); On day 1 and 29 (+/- 5 days): PK blood samples (10 mL) are to be collected within 15 minutes prior to dosing of cabozantinib and at the following time points following ingestion of the dose: 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±15 minutes), and 8 hours (±15 minutes) post-dose.

[7] Optional imaging guided biopsy from an accessible tumor site to be done at baseline, 29 days (+/- 5 days), and at time of progression.

[8] If QTcF interval within normal range at baseline and subsequent ECGs at weeks 3 and 5, then no need for routine ECG monitoring. ECGs may be ordered as needed if there is other clinical indication.

[9] Within 48 hours prior to day 1

[10] Consider 24-hour urine collection for protein if UPCR>1mg/mg

[11] A 50 cc blood sample to be collected for immunologic testing at screening, at week 9 day 1(+/- 5 days), and at progression (+ 5 days). A 10 cc to be collected for pharmacogenetic screening at screening only.

[12] If abnormal at baseline or clinically indicated

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Regular tumor assessments should be performed in accordance to the guidelines in Section 5.5 to determine if PD is present.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

5.3 Post-Treatment Period

Subjects will return to the study site 30 to 37 days after their last dose of cabozantinib to complete end-of-study assessments.

Laboratory and physical examinations will be performed. Remaining study treatment will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects

with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

5.4 Laboratory Assessments

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hematocrit • platelet count • RBC count • hemoglobin	
Serum chemistry		
• albumin • ALP • ALT • AST • bicarbonate • BUN • chloride	• creatinine • Glucose • calcium •	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Other		
• TSH, Free T4 • Pregnancy test (urine or serum) for women of child-bearing potential		• PT/INR or PTT • 24 hour urine collection for protein[a] • Adrenal hormones profile(ACTH, cortisol, aldosterone, plasma renin activity, DHEA-sulfate, testosterone in women, estradiol in men and postmenopausal women) • Mitotane level*

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, INR, International Normalized Ratio; PT, prothrombin time; PTT partial

thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; UPCR, urine protein/creatinine ratio; WBC, white blood cell.

*Only if prior mitotane use within 6 months.

[a] Consider 24-hour urine collection for protein if UPCR>1 mg/mg

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

5.5 Tumor Assessment

Serial imaging studies will be used to assess measurable disease per RECIST 1.1 criteria (9). Contrast-enhanced computerized tomography (CT) scan or magnetic resonance imaging (MRI) of chest/abdomen/pelvis will be obtained every 8 weeks (+/- 5 days) after the start of study drug administration. In patients with IV contrast allergy or borderline renal function, CT without IV contrast or 18 FDG PET CT may be used as clinically indicated.

5.6 Outside Physician Participation During Treatment

- MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
- A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care.
- Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
- Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
- A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
- Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
- The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
- Patients will return to MDACC every 8 weeks for evaluation.

6 SAFETY

6.1 Adverse Events and Laboratory Abnormalities

6.1.1 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. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 6.2.1.

All untoward events that occur after the first protocol intervention through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events according to MDACC standards.

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6.1.2 Serious Adverse Events

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

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

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

6.1.3 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. The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

- Investigator shall notify Exelixis within twenty-four (24) hours of making such discovery by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form;

- This report must be submitted by Institution to Exelixis at e-mail: drugsafety@exelixis.com or fax 650-837-7392, even if it is not felt to be drug related;

- Pregnancy (for a subject or for the partner of a subject), although not itself an SAE, should also be reported on a 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;

- SAEs that must be recorded on an SAE Reporting form include the following:

    - all SAEs that occur after first protocol intervention and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure);

    - any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment;

- although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

6.1.4 Regulatory Reporting

All serious adverse events must be reported to Exelixis using e-SAE form generated by MD Anderson Cancer Center. E-mail: drugsafety@exelixis.com; Fax 650-837-7392.

6.2 Other Safety Considerations

6.2.1 Laboratory Data

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

6.2.2 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. The investigator must inform the MD Anderson IND Office of the 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.

6.2.3 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.

6.2.4 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 decision to discontinue 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 decision to discontinue*** study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

7 STATISTICAL CONSIDERATIONS

7.1 Analysis Population

This is an investigator-initiated, open label, pilot clinical trial to evaluate the efficacy and safety of cabozantinib given in patients with unresectable/metastatic ACC. *The **primary objective** of our study is 4-month progression-free survival (PFS4) rate in patients with unresectable/metastatic ACC who will*

*receive cabozantinib. The **secondary objectives** are to determine the safety and toxicity, overall survival (OS), and to estimate overall response rate (ORR).*

7.1.1 Safety Population

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

7.2 Safety Analysis

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

7.2.1 Adverse Events

Adverse event terms recorded on the eCRFs in the Prometheus database will be mapped to preferred terms using the NCI CTCAE v.4. 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 v4.0. Listings of AEs will be provided.

7.3 Sample Size

This is a pilot clinical trial and is not powered for significance in statistical comparison as there is insufficient existing evidence to predict the likely outcomes. The maximum number of subjects to be recruited for the study is 18.

It is expected for the current trial that the drug will achieve a minimum PFS4 of 20% while the maximum toxicity rate should be below 30%.PFS4 is defined as no disease progression or death within the first 4 months of the proposed treatment. If the trial is not terminated early, a posterior 90% credibility interval for the primary endpoint PFS4 rate will have a width of 0.271, given 3 patients achieving PFS4 under the assumption of 20% PFS4 rate.

7.4 Safety and Futility Monitoring

The PFS4 and toxicity rates will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (10) as extended by Thall and Sung (11), an effective and flexible method which has been successfully applied in hundreds of clinical trials at UT-MD Anderson and other institutions. The prior probabilities of PFS4 and toxicity for the experimental regimen are modeled by beta distributions (*Beta*(0.20, 0.80) and *Beta*(0.25 0.75), respectively). Denoting the probabilities of PFS4 and study drug-related toxicity rate of the experimental treatment by {p(PFS4,E) , p(TOX,E)}, the following decision criteria will be applied:
the trial will be stopped early either due to futility if

$$\text{Prob}\{\, p(\text{PFS4},E) < 0.20 \mid \text{data}\} > 0.90,$$

or due to toxicity if

$$\text{Prob}\{\, p(\text{TOX},E) > 0.25 \mid \text{data}\} > 0.90.$$

The above futility and toxicity monitoring rules will be implemented by a cohort size of 3, starting from the 6th enrolled patient. Patients will be monitored according to the stopping boundaries for PFS4 or study drug-related toxicity specified in **Table 7-1**. For example, the patient enrollment will be stopped if more than 3 severe toxicities (Grade 4) are observed among the first 6 patients. The patient enrollment will continue unless the stopping boundary is reached for evaluable subjects. The corresponding operating characteristics are listed in the **Table 7-2**.

Table 7-1: Stopping boundaries for PFS4 and study-related toxicity

Number of patients evaluated	Stop if # of PFS4 observed	Stop if # of toxicity observed
6	0	4-6

9	0	5-9
12	0-1	6-12
15	0-1	7-15
18	Always stop with this many patients	

Table 7-2: Operating Characteristics (based on simulations from 10,000 trials)

True PFS4 Rate	True Toxicity Rate	Prob (stop the trial early)	Average number of patients treated
0.1	0.10	0.720	10.5
	0.30	0.774	9.9
	0.50	0.930	8.1
0.25	0.10	0.243	15.5
	0.30	0.387	14.2
	0.50	0.809	10.1
0.4	0.10	0.057	17.4
	0.30	0.237	15.9
	0.50	0.763	10.9

The above stopping boundaries were calculated using MultcLean (v.2.1.0) design software (http://biostatistics.mdanderson.org/Software Download).

The Investigator is responsible for completing a Safety/Efficacy Summary Report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 6 evaluable patients per cohort, complete 4 months of study treatment, and every 3 evaluable patients per cohort, thereafter. On every summary submission, toxicity will be assessed after one month, and efficacy after four months of therapy.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "MD Anderson IND Office correspondence".

7.5 Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Additional exploratory subgroup analysis will be conducted if necessary.
Safety data will be reviewed after 6, 9, 12 and 15 patients have completed 1 month of cabozantinib, while efficacy data will be after 6, 9, 12 and 15 patients have completed 4 months of cabozantinib. If the number of PFS4 required for moving the trial to next stage has not been achieved, the patient enrolment will be halted until enough responses observed. Toxicity evaluation will be based on the incidence of severity and type of AEs (including physical and laboratory). Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety.

8 OTHER ANALYSES

Blood samples for pharmacokinetics and pharmacogenetics studies will be collected during study course. However, analysis is planned to occur after data is completely collected, except in the subset of subjects who previously used mitotane within 6 months of study participation. This subset's PK samples will be analyzed shortly after collection to guide cabozantinib dosing.

PK profiles will be obtained on first dose (Day 1) and at steady-state (Day 29 +/- 5 days) after starting study drug. In addition, 1 blood sample will be collected every 12 weeks (+/- 6 weeks) to measure cabozantinib trough levels. If feasible, blood samples will be collected at the time of disease progression or significant toxicity (CTACE grade 3 or more). For determining PK profiles, PK blood samples (10 mL) are to be collected within 15 minutes prior to dosing of cabozantinib and at the following time points following ingestion of the dose: 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±15 minutes), and 8 hours (±15 minutes) post-dose. Blood samples (~10 ml) for the determination of steady-state trough concentrations of cabozantinib will be collected immediately prior to the patient's first dose of the day. The time and date of the patient's prior dose, and time and date of blood sampling will be clearly documented in the patient's medical chart. At each collection point, whole blood (10 mL) will be collected into pre-chilled lavender-top (or similar) collection tubes and immediately placed on wet ice. Within 30 minutes of collection, chilled tubes will be centrifuged at 1,500 x g for 15 min at 4ºC. Plasma (supernatant) will be immediately transferred to pre-labelled cryovials and stored at -80ºC until assayed. Plasma concentrations of cabozantinib will be measured by a validated liquid chromatography-mass spectrometry (LC-MS/MS) assay in a validated laboratory (World Wide Clinical Trials [WWCT], Austin, Texas). All PK samples will be split into two ~2.5 mL plasma samples, with only one (primary) sample being shipped to WWCT for analysis and the other (backup) retained in pre-labelled cryovials and stored at -80ºC. All samples that will be analyzed after study completion will be also stored at -80ºC until assayed.
In most study subjects (estimated 12 out of 18 patients), samples will be analyzed a-posteriori after completing study enrollment. In subjects who were on mitotane therapy within 6 months of study participation, PK samples will be analyzed after collection to allow PK derived dosing as detailed earlier.

Analyses of immune markers in tumor and blood samples: These studies will be performed at MDACC in collaboration with Dr. Ignacio Wistuba who is supervising the Translational Molecular Pathology - Immunoprofiling Laboratory (TMP-IL). Patient samples will be collected to perform immunologic analyses. The study will allow for the collection of blood samples to be drawn at the time of routine blood-draw to assess circulating immune markers. Whole blood, plasma, serum, peripheral blood mononuclear cells (PBMCs) and other secreted markers (such as cytokines) will be collected at 3 time points (before treatment (during screening), at week 9 day 1 visit (+/- 5 days) and at time of disease progression (+ 5 days), and processed at the TMP-IL for further downstream analyses.
Optional biopsies will be used for immune-profiling analysis (core needle biopsies (CNBs). Fresh tissue samples will be sent immediately after collection to TMP-IL. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected, including 2 for clinical processing and 3 additional passes will be attempted to obtain the research core samples. Core biopsy will be performed only when the desired tissue focus is deemed amenable to safe biopsy and low risk for complications.

Cores 1 and 2: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples)

Cores 3-4: Flash freezing in liquid nitrogen.

Core 5: Flow cytometry analysis of TIL and TME on fresh tissue.

All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells to confirm the presence of tumor cells, as well as their abundance (tumor cellularity); b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available for review.

Using immunohistochemistry (IHC) and multiplex immunofluorescence (IF) approach that is available in the TMP-IL (Drs. Wistuba and Jaime Rodriguez Canales), we will quantitatively assess multiple immune markers. Fresh frozen tissues will be also used for analysis of immune markers. IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using the Vectra Inform™ (Perkin-Elmer) software. Nucleic acids (DNA and RNA) and protein extraction: Blood (plasma and PMBCs) and tumor (CNB) samples will be subjected to extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.

High order flow cytometry panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells and their respective receptors such as PD-L1 on infiltrating myeloid cells or tumor. Briefly, 50 cc of heparinized peripheral blood from cancer patients prior to the initiation of treatment, during treatment, and at time of progression will be processed fresh (within 24h of being drawn) for PBMC isolation by ITB. PBMCs will be cryopreserved and stored in Liquid Nitrogen until use. Flow cytometric analysis will be conducted retrospectively on cryopreserved PBMCs. When appropriate, cells will be thawed and stained immediately. All time points belonging to a patient will be stained and acquired at the same time to avoid any technical variation (sample at time of progression will be omitted for responders if analysis needs to be completed when patient is still responding). We expect that half of the study participants will agree to have the optional biopsies and we anticipate to collect blood samples from all participants.

In another exploratory objective, we will attempt to assess the role of genetic variants of drug disposition genes on the PK of cabozantinib. For the past decades, pharmacogenomic association studies have revealed a significant influence of genetic variants on the disposition of various drugs prescribed in the cancer care setting (e.g. tacrolimus, irinotecan, 5-fluorouracil and 6-MP). This continues to be an increasingly popular area of pharmacological research. Cabozantinib is a substrate for both cytochrome P450 3A4 (CYP3A4) and the drug transporter MRP2, and maybe a substrate for other obscure drug metabolizing enzymes and transporters. Hypothetically, single nucleotide polymorphisms (SNPs) in these genes may affect cabozantinib PK. However, there is a dearth of data regarding these potential genetic associations. To preliminary assess for potential associations, a single blood sample (~ 10 ml) will be collected at the patient's first clinic visit for exploratory pharmacogenomic testing. Whole blood will be collected into pre-labelled lavender-top collection tubes. Genomic DNA will be isolated from each blood sample using the GenElute Blood Genomic DNA Kit (Sigma-Aldrich Co), or similar DNA

extraction kit, in the Pharmaceutics Research Laboratory (Division of Pharmacy, Department of Pharmacy Research) by trained research staff. Isolated DNA will be transferred to pre-labelled, de-identified cryovials and frozen at -80ºC in the Pharmacy Research Laboratory freezer prior to shipment. DNA samples will be shipped by research staff in the Pharmacy Research Laboratory to an external laboratory (Avera Institute for Human Genetics, Sioux Falls, SD) for analysis of over 2,000 polymorphisms in drug disposition genes using the powerful DMET™ Plus Array (Affymetrix). Preliminary pharmacogenomic data will be a crucial step towards further understanding the disposition of cabozantinib in cancer patients.

9 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and crosscheck of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. This trial will be monitored by the MDACC IND Office in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The IND office will perform reviews at regular intervals to ensure the validity and integrity of the trial data

10 STUDY COMMITTEES

NA

11 ETHICAL ASPECTS

11.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

11.2 Informed Consent

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

The CRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

11.3 Institutional Review Board/Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC

approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

11.4 Future Use of Patient Samples

No samples for anything other than safety testing will be collected during this study.

12 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications may be made and will be prepared, reviewed, and approved by representatives of the investigator.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (eg, change in monitor or change of telephone number).

13 CONDITIONS FOR TERMINATING THE STUDY

Exelixis reserves the right to terminate the study, and investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

14 STUDY DOCUMENTATION AND RECORDKEEPING

14.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of 2 years following the marketing application approval date for the study treatment in the indication being investigated, 2 years after the investigation is completed or discontinued, or for a time consistent with local regulatory requirements. After that period, the documents may be destroyed subject to local regulations with prior written permission from Exelixis. If the investigator wants to assign the study records to another party or move them to another location, Exelixis must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Exelixis to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a

regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

14.2 Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available, after appropriate notification, to qualified personnel from the Exelixis Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

14.4 Case Report Forms

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

15 MONITORING THE STUDY

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects should be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes and names. The investigator should maintain documents not for submission to Exelixis or designees (e.g., subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to Exelixis and its partners or designees for review.

17 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days before submission and also comply with any provisions regarding publication that are agreed to between the PI's institution (e.g., 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 in accordance to guidelines established by the International Committee of Medical Journal Editors.

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Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all predisease 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 (eg, 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

ECOG, Eastern Cooperative Oncology Group