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| | |
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# A Phase II Study to Evaluate the Effects of Cabozantinib in Patients with Unresectable and Progressive Metastatic Pheochromocytomas and Paragangliomas

**PROTOCOL NUMBER:** 2014-0081

**STUDY DRUG:** Cabozantinib (XL184)

**SPONSOR:** The University of Texas MD Anderson Cancer Center

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# SYNOPSIS

**TITLE**

**A Phase II Study to Evaluate the Effects of Cabozantinib in Patients with Unresectable and Progressive Metastatic Pheochromocytomas and Paragangliomas**

**PROTOCOL NUMBER: 2014-0081**

**CLINICAL PHASE**

Phase II

## RATIONALE

Pheochromocytomas (PHs) and paragangliomas (PGs) are rare neuroendocrine tumors originating in the paraganglia. Approximately 15-20% of these tumors are malignant[1]. Patients with metastatic disease exhibit a decreased overall survival, with only 60% of patients still living five years after initial diagnosis[2]. Malignant PHs and PGs have two characteristics: increased angiogenesis[3] and predilection for bone metastases[4].

*Tumor angiogenesis*

Approximately 50% of patients with malignant PHs and PGs carry germline mutations of the succinate dehydrogenase subunit B *(SDHB)* gene. These mutations prevent oxidative catabolism of succinate into fumarate and electron transport through the internal mitochondrial membrane. As a consequence, production of ATP is attenuated leading to activation of hypoxia-inducible target genes such as vascular endothelial growth factors (*VEGFs)* and the platelet-derived growth factor beta (*PDGF-β*). In addition, genes involved in glucose metabolism such as the hexokinase 2 (*HK2*) and lactate dehydrogenase (*LDH*) are also up-regulated[5]. Activation of these genes causes abnormal and increased tumor angiogenesis, decreased apoptosis, and increased glucose uptake. In fact, $^{18}$F-FDG-PET/CT scan offers 100% sensitivity for the localization of these tumors[6]. Some sporadic tumors exhibit a similar molecular profile[5].

*Bone metastases*

The skeleton is involved in 80% of patients with malignant PHs and PGs[4]. In 20% of these patients, the skeleton is the only location of metastatic spread[4]. Bone metastases are usually lytic and blastic, expansile, and associated with increased morbidity and decreased overall survival[4]. Up to eighty percent of patients with bone metastases develop skeletal related events (SREs) such as: bone pain, fractures, and cord compression that need radiation therapy and/or surgery[4]. Patients experience SREs rapidly once bone metastases are developed (median 4.4 months)[4]. Fifty percent of patients who develop an SRE develop a second SRE within a median of 10 months[4]. Palliative radiation therapy and surgery are frequently required to improve pain and release cord compression. Molecular targeted therapies and chemotherapy may prevent SREs[4].

*Experience with molecular targeted therapies*

A recently published retrospective intention-to-treat study described potential clinical benefits derived from sunitinib in patients with metastatic PHs and PGs[7]. Seventeen patients with progressive disease over a period of 6 months were treated with 37.5-50 mg of sunitinib daily, 4 weeks on, 2 weeks off. Patients were followed with radiographic and biochemical studies every 2 to 3 months. As per RECIST 1.1, 8 patients (47%) exhibited clinical benefits: 3 patients had partial responses and 5 had prolonged stabilization of disease, including 4 patients with extensive skeletal metastases (but not other metastases) identified by $^{18}$F-FDG-PET/CT scan. The tumors that responded to treatment also exhibited more than 30% reduction in glucose uptake 2-3 months after initiation of treatment compared with baseline. Patients who experienced partial response or prolonged stabilization of disease improved blood pressure and some discontinued treatment with antihypertensive medications. Most patients who benefited from sunitinib carried *SDHB* mutations. Unfortunately, most patients who experienced clinical benefits later developed tumor progression[7].

*Hypothesis*

Development of tumor progression and resistance to sunitinib may be related to the compensatory activation of molecular pathways that are not inhibited by this drug, such as the c-MET receptor pathway. MET and VEGFRs cooperate to promote tumor angiogenesis and MET upregulation may occur as a response to the VEGFs pathway inhibition leading to tumor resistance and growth[8]. MET activation is a common feature of human tumors and it is frequently observed in patients with bone metastases[8]. Molecular analyses of malignant PHs and PGs from a few patients participant of phase one clinical trials have found *c-MET* receptor gene mutations (unpublished data). Cabozantinib is a tyrosine kinase inhibitor with antiangiogenic and antitumor activity that targets the VEGF, c-MET, and RET receptors. This drug has been recently approved for the treatment of progressive metastatic medullary thyroid carcinoma another neuroendocrine tumor[9]. Of interest, cabozantinib has also shown effectiveness in patients with castration resistant prostate, breast, and renal cell carcinomas metastatic to the skeleton[10, 11, 12]. Therefore, simultaneous inhibition of MET and VEGFRs by cabozantinib may provide a broad spectrum of antineoplastic activity and prevent tumor resistance in patients with malignant PHs and PGs.

## TARGET POPULATION

Patients with malignant PHs and PGs have metastases into visceral organs and/or the skeleton. Depending on metastases location, the patients can be classified as follows:

1. 40% of the patients have only visceral involvement (liver, lungs, lymph nodules)

2. 40% have visceral and bone metastases
3. 20% have bone metastases only.

Based on this information, we will divide our study population in two different branches:

1. Main branch: 14 patients with measurable disease (+/- bone metastases)
2. Exploratory branch: 8 patients with bone metastases only (+/- small non-measurable lesions).

## OBJECTIVES

The objectives of this study are:

**Primary Endpoint** (14 patients with measurable disease)

To estimate best overall response rate by RECIST 1.1[13] in patients with measurable disease determined by a. CT or b. MRI

**Secondary Endpoints** (All patients)

1. To estimate progression-free survival at 1-year
2. To correlate blood pressure control and change/discontinuation of antihypertensive medications with tumor responses
3. To correlate symptomatology evaluation by the MD Anderson symptom Inventory (MDASI) with tumor responses
4. To correlate plasma metanephrines and chromogranin A with tumor responses
5. To correlate plasma C-reactive protein and interleukin-6 with symptoms and tumor responses
6. Toxicity assessment by the Common Terminology Criteria for Adverse Events (CTCAE)
7. To correlate both c-MET expression by IHC as well as MET amplification by FISH in archived samples and correlate these biomarkers with overall prognosis and responsiveness to cabozantinib.

**Exploratory Endpoints (For patients with only bone metastases n=8)**

1. Best overall response rate in patients with bone metastases only (8 patients) as determined by FDG-PET/CT
2. FDG-PET/CT $SUV_{max}$, advanced volumetric measures including $SUV_{peak}$, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)
3. Time to skeletal related events
4. Incidence of skeletal related events at 4 months and one year
5. Markers of bone turnover (bone specific alkaline phosphatase and CTx)

## STUDY DESIGN

This is a prospective phase II study

## NUMBER OF SUBJECTS

Approximately 22 subjects will be eligible for this study.

## INCLUSION AND EXCLUSION CRITERIA

Malignant PH and PG patients will be eligible for enrollment as defined by the inclusion and exclusion criteria as follows:

Inclusion Criteria

1. 18 years of age or older
2. Histological confirmation of PH/PG
3. Locally advanced or metastatic disease not amenable to surgery
4. Patients enrolled in the main branch should have measurable disease. Patients with a predominance of bone disease who have small, non-measurable or small measurable lesions other than bone, may be included per the principal investigator's discretion, in the exploratory branch of the study for patients with bone metastases only.
5. Progressive disease per RECIST 1.1 as determined by the investigator within the 12 months preceding study enrollment
6. Assessment of all known disease sites, eg, by computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone scan as appropriate, and/or FDG-PET scan within 28 days before the first dose of cabozantinib
7. Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$.
8. Life expectancy of at least 3 months
9. Organ and marrow function and laboratory values as follows within 4 days prior to the first dose of cabozantinib:

    a. Absolute neutrophil count (ANC) $\geq 1500/mm^3$without colony stimulating factor support
    b. Platelets $\geq 100{,}000/mm^3$
    c. Hemoglobin $\geq 9$ g/dL
    d. Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN). For subjects with known Gilbert's disease, bilirubin $\leq 3.0$ mg/dL
    e. Serum albumin $\geq 2.8$ g/dl
    f. Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) $\geq 50$ 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. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis

i. Urine protein/creatinine ratio (UPCR) ≤ 1

j. Serum phosphorus, calcium potassium ≥ LLN and magnesium ≥ 1.2 mg/dL

10. Capable of understanding and complying with the protocol requirements and has signed the informed consent document.

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

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

Exclusion Criteria

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

1. Received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.

2. Prior treatment with cabozantinib

3. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;

4. Received radionuclide treatment (i.e. I $^{131}$ meta-iodo- benzyl guanidine) within 6 months of the first dose of study treatment

5. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment.
6. Receipt of any other type of investigational agent within 28 days before the first dose of study treatment.
7. 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.
8. Prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment.
9. The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
10. The subject requires chronic concomitant treatment of strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).
11. 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 of ≥ 0.5 teaspoon (2.5ml) 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
12. Radiographic evidence of cavitating pulmonary lesion(s)
13. Tumor invading or encasing any major blood vessels
14. 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.
15. Uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
        ii. Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal

antihypertensive treatment within 7 days of the first dose of study treatment

iii. Any history of congenital long QT syndrome

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

- unstable angina pectoris
- clinically-significant cardiac arrhythmias
- stroke (including TIA, or other ischemic event)
- myocardial infarction
- thromboembolic event 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), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis; patients must be completely recovered from these conditions
- malabsorption syndrome

ii. 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.

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

d. Other clinically significant disorders such as:

i. active infection requiring systemic treatment within 28 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 within 7 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.

16. Unable to swallow tablets
17. A corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before first dose of study treatment. Three ECGs must be performed. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.
18. Pregnant or breastfeeding.
19. A previously identified allergy or hypersensitivity to components of the study treatment formulation.
20. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.
21. Evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment except for cured nonmelanoma skin cancer or cured in situ cervical carcinoma
22. 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.

## ESTIMATED LENGTH OF SUBJECT PARTICIPATION

Subjects may continue to receive study treatment until disease progression or as long as the patient is deriving clinical benefit, as judged by the investigator (case-by-case decision with approval of the Medical Monitor), or they experience unacceptable drug-related toxicity.

## ESTIMATED STUDY DATES

First study screening visit: November 2014 to last study follow-up visit July 2020

## INVESTIGATIONAL REGIMEN DOSE/ROUTE/DURATION

Cabozantinib initiation dose is 60 mg daily by mouth

Cabozantinib is supplied as 20-mg and 60-mg tablets.

## COMBINATION DRUG(S)

None

## SAFETY ASSESSMENTS

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) will be performed every 2 weeks for the first 8 weeks followed by assessments every 4 weeks until week 24, then every 8 weeks through week 52, then every 12 weeks. Other safety evaluations including EKGs and urinalysis will be performed at regular intervals.

Adverse event 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) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

## TUMOR ASSESSMENTS

Tumors will be assessed with radiographic studies at baseline and every two months through week 52, and then every 12 weeks:

For patients with measurable visceral metastases CT scans with contrast or MRI are required. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be greater than or equal to 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or greater than or equal to 20 mm when measured by chest x-ray. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT or MRI.

For patients with only bone metastases (Exploratory branch) FDG-PET/CT scan is the only radiographic test required for follow-up. FDG-PET/CT assessment will include standard assessment of $SUV_{max}$, as well as advanced volumetric measures including $SUV_{peak}$, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)

## PHARMACOKINETIC ASSESSMENTS

None.

## BIOMARKER ASSESSMENTS

All patients included in this study will have baseline measurements of resting plasma metanephrines and chromogranin A. Approximately 60% of patients with malignant pheochromocytomas and paragangliomas experience an excessive secretion of catecholamines. In patients with an excessive production of metanephrines at baseline, plasma metanephrines will be obtained every two months. Chromogranin A will be measured at baseline and every two months in all patients. We will correlate biomarkers with overall prognosis, symptoms, and responsiveness to cabozantinib.

Translational Research

1. Deregulation of c-MET can occur via different mechanisms, including gene amplification, overexpression, and activation of somatic mutations, autocrine or paracrine mechanisms, along with interaction of cell surface receptors. c-MET has been found to be over-expressed in a variety of cancers including lung, breast, and ovarian. The most frequent genetic alteration in MET is gene amplification. This amplification has been shown to be associated with a poorer prognosis in certain cancers. The exploratory translational objectives will explore both c-MET expression by IHC as well as MET amplification by FISH and correlate these biomarkers with overall prognosis and responsiveness to cabozantinib. This research will be performed in archived tumor samples.
2. Several symptoms associated with pheochromocytoma and paraganglioma such as fatigue and decreased appetite may be associated with an increased production of Interleukin-6. We will measure c-reactive protein (surrogate biomarker of interleukin-6) and interleukin 6 at baseline and every two months from Day 1. We will correlate these markers with symptoms (MDASI) and overall response to cabozantinib.

## OTHER ASSESSMENTS

c-MET expression by IHC as well as MET amplification by FISH in archived tissue samples

## STATISTICAL METHODS

This Phase II study's primary objective is to estimate the best overall response rate in patients with measurable disease. Response will include RECIST 1.1 CR, PR, and SD. With 14 patients, the 95% confidence interval for a 45% response rate would be (18.9, 71.1%). For the exploratory objective in the small group of patients with bone metastases, the 95% confidence interval for a 45% response rate with 8 patients would be (10.5, 79.5%). We do not include a formal statistical monitoring rule for toxicity given the established safety profile of this drug.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be tabulated by frequencies and the corresponding percentages. Response rates and their 95% confidence intervals will be estimated. Kaplan Meier survival curves will be used to estimate survival outcomes. Cox proportional hazards regression analysis may be used to assess the association between survival and covariates of interest. The Fisher's exact test or logistic regression analysis will be used for any binary outcomes. T-tests or Wilcoxon rank sum tests will be used to compare continuous variables. Longitudinal models may be explored to study change over time.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 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 |
| ESR | erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GABA | γ-aminobutyric acid |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GGT | γ-glutamyl transferase |
| 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 |
| 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:

Pheochromocytomas (PHs) and paragangliomas (PGs) are rare neuroendocrine tumors originating in the paraganglia. Approximately 15-20% of these tumors are malignant[1]. Patients with metastatic disease exhibit a decreased overall survival, with only 60% of patients still living five years after initial diagnosis[2]. Malignant PHs and PGs have two characteristics: increased angiogenesis[3] and predilection for bone metastases[4].

***Tumor angiogenesis***

Approximately 50% of patients with malignant PHs and PGs carry germline mutations of the succinate dehydrogenase subunit B (SDHB) gene. These mutations prevent oxidative catabolism of succinate into fumarate and electron transport through the internal mitochondrial membrane. As a consequence, production of ATP is attenuated leading to activation of hypoxia-inducible target genes such as vascular endothelial growth factors (VEGFs) and the platelet-derived growth factor beta (PDGF-β). In addition, genes involved in glucose metabolism such as the hexokinase 2 (HK2) and lactate dehydrogenase (LDH) are also up-regulated[5]. Activation of these genes causes abnormal and increased tumor angiogenesis, decreased apoptosis, and increased glucose uptake. In fact, 18F-FDG-PET/CT scan offers 100% sensitivity for the localization of these tumors[6]. Some sporadic tumors exhibit a similar molecular profile[5].

***Bone metastases***

The skeleton is involved in 80% of patients with malignant PHs and PGs4. In 20% of these patients, the skeleton is the only location of metastatic spread[4]. Bone metastases are usually lytic and blastic, expansile, and associated with increased morbidity and decreased overall survival[4]. Up to eighty percent of patients with bone metastases develop skeletal related events (SREs) such as: bone pain, fractures, and cord compression that need radiation therapy and/or surgery[4]. Patients experience SREs rapidly once bone metastases are developed (median 4.4 months)[4]. Fifty percent of patients who develop an SRE develop a second SRE within a median of 10 months[4]. Palliative radiation therapy and surgery are frequently required to improve pain and release cord compression. Molecular targeted therapies and chemotherapy may prevent SREs[4].

***Experience with molecular targeted therapies***

A recently published retrospective intention-to-treat study described potential clinical benefits derived from sunitinib in patients with metastatic PHs and PGs[7]. Seventeen patients with progressive disease over a period of 6 months were treated with 37.5-50 mg of sunitinib daily, 4 weeks on, 2 weeks off. Patients were followed with radiographic and biochemical studies every 2 to 3 months. As per RECIST 1.1, 8 patients (47%) exhibited clinical benefits: 3 patients had partial responses and 5 had prolonged stabilization of disease, including 4 patients with extensive skeletal metastases (but not other metastases) identified by18F-FDG-PET/CT scan. The tumors that responded to treatment also exhibited more than 30% reduction in glucose uptake 2-3 months after initiation of treatment compared with baseline. Patients who experienced partial response or prolonged stabilization of disease improved blood pressure and some discontinued treatment with antihypertensive medications. Most patients who benefited from sunitinib carried SDHB mutations. Unfortunately, most patients who experienced clinical benefits, later developed tumor progression[7].

***Hypothesis***

Development of tumor progression and resistance to sunitinib may be related to the compensatory activation of molecular pathways that are not inhibited by this drug, such as the c-MET receptor pathway. MET and VEGFRs cooperate to promote tumor angiogenesis and MET upregulation may occur as a response to the VEGFs pathway inhibition leading to tumor resistance and growth8. MET activation is a common feature of human tumors and it is frequently observed in patients with bone metastases[8]. Molecular analyses of malignant PHs and PGs from a few patients participant of phase one clinical trials have found c-MET receptor gene mutations (unpublished data). Cabozantinib is a tyrosine kinase inhibitor with antiangiogenic and antitumor activity that targets the VEGF, c-MET, and RET receptors. This drug has been recently approved for the treatment of progressive metastatic medullary thyroid carcinoma another neuroendocrine tumor[9]. Of interest, cabozantinib has also shown effectiveness in patients with castration resistant prostate, breast, and renal cell carcinomas metastatic to the skeleton[10, 11, 12]. Therefore, simultaneous inhibition of MET and VEGFRs by cabozantinib may provide a broad spectrum of antineoplastic activity and prevent tumor resistance in patients with malignant PHs and PGs.

## 1.2 Cabozantinib (XL184)

### 1.2.1 Pharmacology

Cabozantinib is a potent inhibitor of multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, version 9, 2013). 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.

RTKs regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair[14]. 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)[14]. c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (e.g., renal tubular cells, gland formation, etc.), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells in vitro and metastases in vivo (Investigator's Brochure, version 9, 2013). 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[14]. Principal investigator unpublished data has shown somatic c-met mutations in patients with metastatic PHs and PGs.

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity[15], either by means of c-Met kinase overexpression[15], activating c-Met gene mutations and/or amplification[16, 17, 18], or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF[19, 20].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[19].

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability[21]. 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[22]. High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (i.e., therapy-resistant) breast cancer and poor survival. VEGFR2 is highly expressed in malignant PH and PGs[23,24]. In preclinical studies anti-angiogenic medications such as sunitinib induced apoptosis of pheochromocytoma cells by inhibiting VEGFR-2/AKT/mTOR pathway.

### 1.2.2 Cabozantinib Nonclinical Toxicology

In rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues, bone, and pancreas (Investigator's Brochure, version 9, 2013). Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, and decreased fertility in male and female rats. The carcinogenic potential of cabozantinib has not been evaluated.

### 1.2.3 Clinical Experience

Analysis of safety and clinical responses data in 1311 subjects treated with cabozantinib in company-sponsored single-agent studies (XL184-001, XL184-008, XL184-201,

XL184-203, XL184-205, and XL184-301 [cabozantinib arm]) has been performed. The data cut-off for this analysis is February 28, 2013 (Investigator Brochure, Version 9, 2013). A summary of this analysis is presented here.

#### 1.2.3.1 Clinical Summary

***Phase I Studies***

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

In **Study XL184-002,** treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2013 Investigator's Brochure Version 9.

In **Study XL184-008** which was mostly a clinical pharmacology study, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of daily dosing of 175 mg cabozantinib and a single dose of rosiglitazone has been by comparing the PK profile of a single dose of rosiglitazone before and after administration of ≥ 21 daily doses of cabozantinib at ≥ 100 mg/day FBE weight (125 mg malate salt weight). The PK of cabozantinib when combined with a single dose of rosiglitazone was also evaluated. Secondary and exploratory objectives of Study XL184-008 were to evaluate the safety and tolerability of cabozantinib and antitumor efficacy in subjects with relapsed or refractory RCC. Twenty-five subjects with RCC were enrolled in the study. Half of the subjects had 1-2 lines of prior therapy with systemic agents, and the other half had 3 or more lines of prior therapy. The majority of subjects (88%) had prior anti-VEGF

anticancer therapies. Of the 25 evaluable subjects at Week 16, seven subjects (28%) achieved PRs, 13 subjects had SD (52%), and one subject (4%) had PD as best response. The median PFS was 12.9 months (95% CI: 9.9, not applicable) (data on file). The median OS was not yet reached with median follow-up of 14.7 months (range: 11.2-21.8 months). In patients with DTC, PFS has not been reached. A DCR of 73% at 24 weeks has obtained (Investigator Brochure, Version 9, 2013).

**Study XL184-014** is a phase 1 study currently active in Japan. The study includes subjects with advanced solid tumors enrolled in successive cohorts to receive cabozantinib administered PO as capsules or tablets in a 3+3 trial design. Subjects are treated with continuous 4-week cycles of cabozantinib administered PO qd. Response is assessed on Day 29 and every 8 weeks thereafter by modified Response Evaluation Criteria inn Solid Tumors (mRECIST) v1.0 criteria. A total of 23 subjects with advanced malignancies have been enrolled: NSCLC (n = 9); gastrointestinal stromal tumor (n = 4); colorectal cancer (n = 4), pancreatic cancer (n = 2), leiomyosarcoma, duodenal cancer, MTC, and thymic cancer (n = 1, each). Four of five heavily pre-treated subjects with NSCLC have had a confirmed PR. Of the four subjects with PRs genetic evaluation revealed that one subject had an EGFR mutation, one subject was RET-fusion positive, and two subjects were ALK fusion positive (Investigator Brochure, Version 9, 2013)..

**Study XL184-202** was a phase 1b/2 trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase 1 dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A PR was observed in 5 subjects (8%). The ORR for the Phase 1 population was 8.2% (90% CI: 3.3, 16.5). The median PFS for subjects (mITT Population) was 3.68 months (95% CI: 3.15, 5.49). The Kaplan-Meier estimate of the probability of a subject to be progression-free at 6 months was 29.4% (Investigator Brochure, Version 9, 2013). Twenty-eight subjects were enrolled in the Phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced PD receive single-agent cabozantinib or cabozantinib in combination with erlotinib. A PR was observed in one subject who was treated with single-agent cabozantinib. The ORR for subjects who received cabozantinib was 6.7% (90% CI: 0.3, 27.9). No objective

responses were seen in subjects who received cabozantinib + erlotinib (0/13 subjects). The median PFS for subjects (mITT Population) was 1.91 months (95% CI: 1.64, 7.06) for the cabozantinib arm and 3.94 months (95% CI: 1.54, 7.26) for the cabozantinib + erlotinib arm. The Kaplan-Meier estimate of the probability of a subject to be progression-free at 6 months was 30.8% for the cabozantinib arm and 22.0% for the cabozantinib + erlotinib arm (Investigator Brochure, Version 9, 2013).

***Phase 2 Studies***

In study **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib daily as a single agent. Group A received an initial dose of 140 mg (175 mg malate salt weight) (Group A), subsequent cohorts (Groups B and C) received an initial dose 100 mg (125 mg of malate salt weight). Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Study objectives included assessments of safety, tolerability, and clinical activity (consisting of independent radiology facility [IRF]-determined response assessment and PFS), at the two dose levels. Enrollment of this study has been completed. Analysis is ongoing (Investigator Brochure, Version 9, 2013).

**Study XL184-203** is a phase 2 randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastro esophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg daily for 12 weeks. Primary endpoints were objective response rate (ORR) at Week 12 and PFS in the Randomized Stage. An Independent Data Monitoring Committee (IDMC) monitored safety in the blinded Randomized Stage. As of October 2011, all subjects have been unblinded.

In 116 CRPC subjects evaluable for post-baseline bone scan changes, best assessments of bone scan improvement were observed in 79 subjects (68%), including complete resolution (100% reduction of bone scan lesion area [BSLA]) in 14 subjects (12%) and partial resolution (≥30% reduction of BSLA) in 65 subjects (56%); SD by bone scan was

observed in 33 subjects (28%), and PD by bone scan (≥ 30% increase in BSLA) in four subjects (3%). Based on a retrospective survey completed by investigators, the majority of the subjects reported reduced bone pain and reduced reliance upon narcotic pain medication. There were 83 subjects with bone metastases and bone pain at baseline who had at least one post-baseline assessment of pain status. Of these, 56 subjects (67%) had pain improvement at either Week 6 or 12. There were 71 subjects who required narcotic analgesic medication at baseline for control of bone pain. Among the 55 subjects who were evaluable for post-baseline changes in consumption of narcotics, 31 (56%) were able to decrease or discontinue narcotic medication (Investigator Brochure, Version 9, 2013).

Bone scan improvement was associated with other measures of antitumor effect and clinical benefit. Relative to subjects with either stable or progressive bone scans, more subjects with complete or partial bone scan resolution had regression of measurable soft tissue disease (81% vs 61%), substantial declines in CTx, a marker of bone turnover (62% vs 48%), pain relief (93% vs 35%), reduced narcotic use (72% vs 23%), and a higher rate of PFS at 6 months (56% vs 41%). Changes in prostate-specific antigen (PSA) appeared to be independent of radiographic changes (Investigator Brochure, Version 9, 2013).

Two dosing cohorts, 100 mg (N = 93) and 40 mg (N = 51) once daily, were examined in the CRPC NRE. The primary endpoint for the CRPC NRE was BSR prospectively assessed by an IRF using a computer-assisted detection (CAD) system. Partial BSR was defined as ≥30% reduction of BSLA (Investigator Brochure, Version 9, 2013) and complete BSR as 100% resolution of the BSLA. Progressive disease (PD) was defined as ≥ 30% increase in BSLA. Subjects with IRF identified measurable soft-tissue lesions on baseline CT or MRI scans were evaluated for BOR by RECIST 1.1.

Prospective measurement of subjects' pain and narcotic use at baseline and throughout the study was obtained by patient reports through standardized tools (BPI over IVRS and paper pain medication diaries) over 7-day reporting intervals. Bone scan responses in evaluable individuals were observed in 67% (100 mg) and 49% (40 mg) of patients. Soft tissue regression was observed in 80% (100 mg) and 79% (40 mg) of evaluable

individuals. Pain improved in 67% of patients. This improvement led to a substantial reduction of narcotics dose (Investigator Brochure, Version 9, 2013).

**Study XL184-205** is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 20 mg (25 mg malate salt weight) daily (Arm 1) continuously, 60 mg (75 mg malate salt weight) daily) (Arm 2) continuously, and 100 mg (125 mg malate salt weight) daily for 2 weeks followed by 40 mg (50 mg malate salt weight) daily continuously (Arm 3), and 100 mg (125 mg malate salt weight) daily on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. No analysis of clinical activity was performed for this study (Investigator Brochure, Version 9, 2013).

***Phase 3 studies***

**Study XL184-301 (EXAM trial)** is a blind, multicenter, controlled trial for subjects with unresectable, locally advanced or metastatic MTC. In this study, 330 subjects with unresectable, locally advanced or metastatic MTC were randomized 2:1 to receive either cabozantinib 140 mg (175 mg malate salt weight) or placebo administered qd in a double-blinded fashion (219 cabozantinib, 111 placebo). Subjects were required to have documented radiographic disease progression per mRECIST within 14 months prior to randomization. The primary objective of this study was to determine PFS in subjects treated with cabozantinib compared with placebo. Key secondary objectives were to evaluate overall response rate and OS. An IDMC evaluated interim safety and efficacy data from this study to protect subject welfare and to identify issues and provide recommendations regarding the study design and conduct. Enrollment in this study has been completed. Of the enrolled subjects, 323 received study treatment (214 cabozantinib, 109 placebo). In October 2011, the study was unblinded and the data analyzed and assessed for the primary endpoint. At the data cut-off date for the primary analysis of efficacy and safety, 113 subjects (98 cabozantinib, 15 placebo) were still on study treatment. A subsequent 120-Day Safety Report (XL184-301 Safety Addendum) was generated with a data cut-off date of 31 December 2011; at that data cut-off there were 73 subjects (65 cabozantinib, 8 placebo) still on study treatment.

The median PFS was significantly longer in the cabozantinib-treated patients (11.2 months) compared with the placebo group (4.0 months) with a response rate of 28% for cabozantinib but 0% in placebo-treated patients. Responses were observed regardless of

RET mutation status and correlations of radiologic response were made with changes in calcitonin and CEA levels from baseline[26]. Findings from this study led to the approval of cabozantinib in the US by the FDA in November 2012 for patients with progressive, metastatic MTC.

**Study XL184-307 (COMET-1)** is a randomized, double-blind, active comparator-controlled study (COMET-1), subjects with metastatic CRPC with bone-dominant disease who have experienced disease progression on both docetaxel-containing chemotherapy and abiraterone or enzalutamide are randomized 2:1 to receive cabozantinib 60 mg or prednisone (or prednisolone in some countries) in a double-blinded fashion. The objective of this study is to evaluate the effect of cabozantinib compared with prednisone on OS. No clinical activity data are currently available for this study (Investigator Brochure, version 9, 2013).

**Study XL184-306 (COMET-2)** is a randomized, double-blind, active comparator-controlled study; subjects with previously treated symptomatic CRPC are randomized 1:1 to receive cabozantinib 60 mg or a combination regimen of mitoxantrone plus prednisone. The primary objective of this study is to evaluate the effect of cabozantinib on pain palliation in subjects with bone metastases and pain related to bone metastases despite narcotic use; secondary endpoints are BSR and OS. No clinical activity data are currently available for this study (Investigator Brochure, version 9, 2013).

***Expanded Access Study***

**Study XL184-209** enrolled three subjects with progressive, metastatic MTC in order to have access to cabozantinib during review by the FDA and before commercial availability of cabozantinib. Following FDA approval of cabozantinib and the subsequent availability of commercial drug, the study was closed to enrollment, and the remaining subjects rolled over to commercial drug. No analysis of clinical activity data will be performed for this study. (Investigator Brochure, Version 9, 2013)

***Maintenance Study***

**Study XL184-900** is a maintenance study in which subjects from studies of cabozantinib given as a single-agent, or in combination with erlotinib or with TMZ may enroll. The objectives of this study are: 1) to allow subjects who are currently benefitting from cabozantinib treatment as a single-agent or in combination, and who are enrolled in cabozantinib studies that are closing, to continue to receive cabozantinib treatment; and 2) to further characterize the long-term safety and tolerability of cabozantinib. Subjects who roll over to this study will continue to receive the same doses of cabozantinib and any combination therapy that they are receiving on their current study. As of the 28 February 2013 data cut-off, 34 total subjects had rolled over into the XL184-900 Study from six other XL184 studies; 8 from XL184-001, 1 from XL184-002, 14 from XL184-008, 5 from XL184-201, 3 from XL184-202, and 3 from XL184-205. No clinical activity data are available from this study (Investigator Brochure, Version 9, 2013).

#### 1.2.3.2 Clinical Safety Profile

Through 28 February 2013, 1311 subjects with cancer had been treated with single-agent cabozantinib in open-label or unblinded company-sponsored clinical trials. The subjects in that data set were predominately White (87.9%) and male (64.9%) with a median age of 61.0 years (Investigator Brochure, Version 9, 2013).

In Study XL184-301, 323 subjects with MTC have been treated with single-agent cabozantinib (n=214) or placebo (n=109). The subjects in that data set were predominately White (cabozantinib arm, 89.7%; placebo arm, 89.9%) and male (cabozantinib arm, 69.6%, placebo arm, 63.3%) with a median age of 55.0 years (both arms).

Based on data available in the safety addendum of placebo-controlled Study XL184-301 (data cut-off 31 December 2011), the median duration of exposure was 315.0 days (10.35 months) and 104.0 days (3.42 months) in cabozantinib-treated subjects and placebo-treated subjects, respectively. Twenty-five percent of subjects in the cabozantinib arm had duration of exposure of 440 days or more compared with 187 days or more in the placebo arm. This suggests that cabozantinib treatment is tolerated for prolonged periods of time.

Dose modifications (reduction or delay) were frequent in the cabozantinib arm of this study. Most (80.8%) cabozantinib-treated subjects had a 1-level dose reduction from 140 mg FBE weight (175 mg malate salt weight) to 100 mg (125 mg malate salt weight) , and 43.9% had a 2-level dose reduction from 100 mg to 60 mg (75 mg malate salt weight). In comparison, 11.0% of placebo-treated subjects had a 1-level dose reduction, and 0.9% had a 2-level dose reduction. Overall, one or more dose delays due to an AE occurred in 68.7% of cabozantinib-treated subjects compared with 17.4% of placebo-treated subjects. The median duration of these dose delays was 4.0 days and 8.0 days in cabozantinib-treated and placebo-treated subjects, respectively (Investigator Brochure, Version 9, 2013).

While all subjects were initially treated with a dose of 140 mg, subjects' final recorded dose levels as of discontinuation or the data cut-off were distributed over the three protocol-permitted dose levels in the study (140, 100, and 60 mg qd), reflecting the use of protocol-defined dose modifications to manage AEs and adjust the dose of each subject to his or her degree of tolerance of the study drug. There was a wide range of duration of treatment at all dose levels including at the 140 mg dose (Investigator Brochure, Version 9, 2013).

#### 1.2.3.2.1 Adverse Events

***Adverse Events in Subjects with Solid Tumors Treated with Cabozantinib as Single Agent (Pooled Single-Agent, Open-Label Studies)***

The most frequently (≥ 20%) observed AEs in 1311 patients participant in single agent studies as of February 28, 2013 regardless of causality, were fatigue: (66.7%), diarrhea (63.1%), decreased appetite (51.9%), nausea (51.9%), weight decreased (36.0%), PPES (35.9%), vomiting (34.1%), constipation (33.2%), dysgeusia (28.0%), hypertension (27.8%), dysphonia (26.3%), abdominal pain (23.3%), aspartate aminotransferase (AST) increased (23.0%), dyspnea (21.3%), headache (20.9%), rash (20.4%), and ALT increased (20.2%). The safety profile of single-agent cabozantinib is consistent across tumor types (Investigator Brochure, version 9, 2013).

The most frequently (≥ 20%) observed AEs reported as related to cabozantinib, were fatigue (60.0%), diarrhea (56.1%), decreased appetite (44.1%), nausea (42.4%), PPES

(35.6%), weight decreased (29.1%), dysgeusia (27.1%), hypertension (24.0%), vomiting (23.5%), dysphonia (22.0%), and AST increased (20.1%).
The most common AEs (≥ 5%) reported at severity of Grade 3 and above include fatigue (15.9%), diarrhea (11.1%), hypertension (9.7%), PPES (8.9%), lipase increased (6.8%), PE (5.9%), abdominal pain (5.5%), decreased appetite (5.3%), and asthenia (5.0%)(Investigator Brochure, version 9, 2013).

***Adverse Events in Subjects with MTC Treated with Cabozantinib as Single Agent Compared with Placebo (XL184-301)***

The cut-off date for AE data comparing the two treatment arms, cabozantinib versus placebo, in Study XL184-301 was 28 February 2013 (Investigator Brochure, Version 9, 2013). The most frequent AEs (≥ 30% incidence) in cabozantinib-treated subjects were diarrhea (69.6% in cabozantinib-treated subjects vs 35.8% in placebo-treated subjects), weight decreased (55.6% vs 11%), palmar-plantar erythrodysesthesia syndrome (52.3% vs 1.8%), decreased appetite (48.6% vs 15.6%), nausea (45.8% vs 21.1%), fatigue (41.6% vs 30.3%), dysgeusia (34.6% vs 5.5%), hair color changes (33.6% vs 0.9%), and hypertension (30.8% vs 4.6%).

#### 1.2.3.2.2 Serious Adverse Events

***Serious Adverse Events in Subjects with Solid Tumors Treated with Cabozantinib as Single Agent (Pooled Single-Agent, Open-Label Studies)***

The most commonly reported SAEs (≥ 2%) were pulmonary embolism (5.1%), vomiting (3.4%), dehydration (3.2%), pneumonia (3.0%), nausea (3.0%), abdominal pain (2.4%), diarrhea (2.4%), deep vein thrombosis (DVT; 2.1%), and convulsion (2.0%)(Investigator Brochure, version 9, 2013).

***Serious Adverse Events in Subjects with MTC Treated with Cabozantinib as Single Agent Compared with Placebo (XL184-301)***

The most commonly reported SAEs (≥ 2%) occurring on the cabozantinib-treatment arm of Study XL184-301 were pneumonia (4.2%), pulmonary embolism (3.3%), mucosal

inflammation (2.8%), hypocalcemia (2.8%), dysphagia (2.3%), and dehydration (2.3%)(Investigator Brochure, version 9, 2013).

#### 1.2.3.2.3 Deaths

As of 28 February 2013, 192 fatal SAEs were reported (182 on single-agent cabozantinib or cabozantinib in combination with other therapies, 10 on placebo) across all open-label or unblinded company-sponsored studies (Studies evaluated include XL184-001, XL184-002, XL184-008, XL184-014, XL184-201, XL184-202, XL184-203, XL184-205, XL184-209, XL184-900, and all clinical pharmacology studies (n=1754). The majority of these SAEs were attributed to disease progression (70.3%) (Investigator Brochure, Version 9, 2013).

Fifty-seven subjects had fatal SAEs that were attributed to reasons other than PD. 53 subjects received cabozantinib and four received placebo. Of the 53 cabozantinib-treated subjects, 27 had events assessed as related to cabozantinib study treatment (24 as a single agent, 3 in combination with erlotinib) and 26 subjects had events attributed to reasons other than PD or study treatment (20 as a single agent, 6 in combination with other therapies). Fatal side effects not attributed to disease progression for Cabozantinib-treated subjects on open-label or unblinded studies include single cases of GI hemorrhage, hemoptysis, PE, intestinal perforation, enterocutaneous fistula, diverticular perforation, and peritonitis, 3 patients who had intracranial hemorrhage, and 4 cases who died of respiratory failure (Investigator Brochure, Version 9, 2013).

### 1.1.1.4 Clinical Pharmacokinetics

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%) (Investigator Brochure, Version 9, 2013).

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. A PK study of cabozantinib in patients with renal impairment (XL184-017) is ongoing. The results of a population PK analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib. The PK evaluation of cabozantinib in subjects with hepatic impairment (XL184-003) is ongoing; preliminary data suggest that subjects with mild hepatic function impairment (Child-Pugh A) show a 59% higher plasma AUC0-∞ for cabozantinib as compared with matched healthy subjects. 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 (Investigator Brochure, Version 9, 2013).

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the cabozantinib N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin (Investigator Brochure, Version 9, 2013).

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in HLM preparations. IC50 values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib at steady-state plasma concentrations (≥100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in patients with solid tumors (Investigator Brochure, Version 9, 2013).

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 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 (Investigator Brochure, Version 9, 2013).

Cabozantinib is an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells (Investigator Brochure, Version 9, 2013).

#### 1.1.1.5 Clinical Activity

In the placebo-controlled Phase 3 study XL184-301 in 330 MTC subjects, a significant increase in median PFS was seen in the cabozantinib arm compared with placebo (11.2 vs 4.0 months; hazard ratio [HR] =0.28; 95 CIs: 0.19, 0.40). Confirmed PRs occurred in 28% of cabozantinib-treated subjects and none in the placebo arm; responses were durable (median duration 14.6 months)[26]. An unplanned administrative analysis of overall survival (OS) performed at the request of the FDA with a data cut-off of 15 June 2012 (75% of required deaths) showed a trend for improved duration of OS in the cabozantinib arm compared with placebo (26.0 months vs 20.3 months; HR = 0.83; 95% CI: 0.60, 1.14). In the Phase 1 Study XL184-001, with an enriched MTC population, PRs were reported in 29% of 35 MTC subjects with measurable disease across all dose levels and in 28% of 25 MTC subjects treated at the MTD. The median duration of treatment for the subjects in Study XL184-001 with PRs was 17.7 months with one subject receiving treatment for 68.4 months on XL184-001 before rolling over onto maintenance trial XL184-900 to continue to receive cabozantinib[25].

In addition to MTC, cabozantinib has demonstrated findings consistent with broad clinical anti-tumor activity in early Phase 1 and Phase 2 studies in several other tumor

types. In a randomized discontinuation trial (RDT) XL184-203, the following disease control rates (DCR = complete response [CR] + partial response [PR] + stable disease [SD]) at Week 12 were observed in tumor types including non-small cell lung cancer (NSCLC), 38%; breast cancer, 48%; melanoma, 46%; ovarian cancer, 53%; hepatocellular carcinoma (HCC), 66%; and CRPC, 66%. In Study XL184-008, clinical activity was also observed in differentiated thyroid cancer (DTC; DCR = 73% at 24 weeks) and renal cell carcinoma (RCC; median progression-free survival [PFS] = 12.9 months). Observations of clinical activity have included decrease of soft tissue tumor lesions including visceral metastases, effects on metastatic lesions on bone scan (partial or complete bone scan resolution), reduction in serum markers of bone resorption and formation, reduction in circulating tumor cells (CTCs) in subjects with prostate cancer with increases in hemoglobin, and improvements in bone pain and reductions in narcotic use in subjects with bone metastases (Investigator Brochure, Version 9, 2013).

In the Phase 2 study XL184-203, cabozantinib demonstrated broad clinical activity in men with CRPC (Smith et al. 2013). During the RDT phase, the majority of CRPC subjects with bone metastases and elevated total alkaline phosphatase (t-ALP) levels at baseline showed reductions in t-ALP[26]. Similarly, during the non-randomized expansion (NRE) phase, the majority of CRPC subjects at the 100 mg assigned dose showed reductions in circulating bone specific alkaline phosphatase (BSAP)[27]. These effects were independent of prior or concomitant bisphosphonate treatment. Reductions in bone biomarkers were also evident in the 40 mg CRPC NRE cohort (Investigator Brochure, Version 9, 2013). Effects on bone scan were assessed by an independent reader, and pain and narcotic use were prospectively assessed using an interactive voice recording system (IVRS) and a diary. Subjects achieved a bone scan response (BSR) in both the 100 mg and 40 mg assigned NRE dose cohorts (67% and 49%, respectively). Among subjects with baseline pain of at least 4 (0-10 scale by Brief Pain Inventory [BPI]), a majority had at least a decrease of 30% in the average daily worst pain compared with baseline in both cohorts (100 mg: 64% of subjects; 40 mg: 69% of subjects). In addition, more than half of subjects decreased narcotic use (Investigator Brochure, Version 9, 2013).

#### 1.1.1.6 Translational Medicine

*RET mutations*

Of the 36 subjects tested in the XL 184-001 study, 67% were found to harbor *RET* mutations in either blood or tumor samples. Of the remaining 12 subjects, three (8%) of the subjects showed no evidence of *RET* mutation in either tumor or blood samples, and 9 (25%) subjects had inadequate data. These results confirmed the high rate of *RET* mutations associated with this disease. Of the three subjects showing no evidence of *RET* mutation in either tumor or blood samples, two achieved PR (one confirmed) and one showed PD as best response, indicating that mutations in *RET* may not be necessary for clinical benefit from treatment with cabozantinib.

Serial skin biopsies from a patient with MTC enrolled in the expanded MTD (eMTD) Cohort and were analyzed using fluorescence-based IHC. Levels of phosphorylated targets of cabozantinib, MET, RET, and KIT, were significantly decreased (40%, 40%, and 61%, respectively). In addition, decreases in key downstream mediators of cabozantinib target receptors were also measured; pERK and pAKT showed decreases of 55% and 39%, respectively. These effects are similar to those observed inpreclinical experiments[28], indicating that exposure to cabozantinib results in consistent changes in target signaling pathways.

In the study XL 184-301 (EXAM trial), archival tumor samples to determine *RET* mutational status in tumors and a whole blood sample to determine hereditary *RET* status were collected. *RET* status was determined in 65% (215/330) of the enrolled subjects. Of these 215 subjects, 79% had activating *RET* mutations and 21% had no *RET* mutations detected. Of 85 evaluated subjects with either no *RET* mutations or unknown RET status, 16 were found to have a *RAS* gene mutation. Cabozantinib had activity across all *RET* and *RAS* mutational subgroups, and demonstrated response rates of 22-32%, consistent with the response rate of subjects in the study overall. Subjects with *RET* mutations had significantly longer median PFS (60 weeks) than subjects who were *RET* mutation-negative (25 weeks). Subjects with *RAS* mutations had a median PFS of 47 weeks, indicating that clinical activity measured in the *RET* mutation-negative subgroup can be attributed partially to subjects with *RAS* mutations (Investigator Brochure, Version 9, 2013).

*BRAF*

Preliminary analysis of 48 melanoma subjects with both tumor response and BRAF mutation data suggests that the clinical activity of cabozantinib is independent of BRAF mutation status(Investigator Brochure, Version 9, 2013).. Clinical activity of

cabozantinib also appears to be independent of epidermal growth factor receptor (EGFR) and KRAS mutation status in NSCLC subjects based on the preliminary data (Investigator Brochure, Version 9, 2013).

*Biomarkers of response of anti-angiogenic therapies*

Plasma samples from patients with GB (XL-184-201) were analyzed for several biomarkers of response to anti-angiogenic agents, including levels of VEGF-A, sVEGFR2, and PlGF. Changes in pharmacodynamic markers consistent with cabozantinib on-target effects were observed after cabozantinib administration in 40 subjects treated with a starting dose of 140 mg FBE weight (175 mg malate salt weight). Changes in PlGF (↑), VEGF-A (↑), sVEGFR2 (↓), and soluble KIT (sKIT)(↓) reached statistical significance at multiple time points, particularly Days 15 and 29. Soluble MET as a potential biomarker of MET inhibition was modulated (↑) upon cabozantinib treatment and changes reached statistical significance as well, on Day 15 and Day 57 (Cycle 3 Day 1) (Investigator Brochure, Version 9, 2013).

In the study XL 184-301 (EXAM trial), exposure to cabozantinib resulted in significant decreases in the levels of the circulating sVEGFR2 and sKIT, consistent with results observed in other cabozantinib studies and with other anti-VEGFR2 inhibitors, and a modest but statistically significant relationship between plasma cabozantinib exposure and pharmacodynamic response was apparent (Investigator Brochure, Version 9, 2013).

*Markers of bone turnover*

Circulating CTx was reduced in the majority of CRPC patients included in the XL-184-203 study[26]. Similar changes were seen in NTx. These effects of cabozantinib on circulating CTx and NTx levels appear to be independent of prior or concomitant bisphosphonate treatment or presence of bone metastases[27]. Consistent with effects of cabozantinib on osteoblast activity, the majority of CRPC RDTsubjects with bone metastases and elevated t-ALP levels at baseline showed reductions in t-ALP (Investigator Brochure, Version 9, 2013). Similarly, the majority of CRPC NRE subjects at the 100 mg assigned dose showed reductions in circulating BSAP[26]. These effects were independent of prior or concomitant bisphosphonate treatment. Reductions in bone biomarkers were also evident in the 40 mg CRPC NRE cohort: the median change in CTx at Week 12 was a 31% reduction and 50% of evaluable patients exhibited a decrease in BSAP at week 12 or later (Investigator Brochure, Version 9, 2013).

*Circulating tumor cells*

In metastatic prostate cancer, CTC counts at baseline have prognostic value, and changes on therapy have been considered to be predictive of treatment benefit[29]. For the 100 mg CRPC NRE cohort, robust reductions in CTCs were observed regardless of prior therapy in 62 subjects with baseline CTC counts ≥ 5/7.5 mL of blood and a Week 6 and/or Week 12 assessment. Fifty-seven subjects (92%) had ≥ 30% decrease in their CTC count, while 39% of evaluable subjects converted to < 5 CTCs at Week 6[27]. Similarly, for the 40 mg CRPC NRE cohort, reductions in CTCs were observed regardless of prior therapy in 39 subjects with baseline CTC counts ≥ 5/7.5 mL of blood and a Week 6 and/or Week 12 assessment: 67% demonstrated CTC decrease ≥30% in their CTC count, while 22% of evaluable subjects converted to <5 CTCs at Week 6 (Investigator Brochure, Version 9, 2013).

**1.3 Study Population,**

**1.3.1 Study Population for the Study:**

Patients with malignant PHs and PGs have metastases into visceral organs and/or the skeleton. Depending on metastases location, the patients can be classified as follows:

40% of the patients have only visceral involvement (liver, lungs, lymph nodules)

40% have visceral and bone metastases

20% have bone metastases only.

Based on this information, we will divide our study population in two different branches:

- Main branch: 14 patients with measurable disease (+/- bone metastases)
- Exploratory branch: 8 patients with bone metastases only (+/- small non-measurable lesions).

# 2 STUDY OBJECTIVES AND DESIGN

## 2.1 Study Objectives

The objectives of this study are as follows:

**Primary Endpoint (14 patients with measurable disease)**

To estimate best overall response rate by RECIST 1.1[13] in patients with measurable disease determined by a. CT or b. MRI

**Secondary Endpoints (All patients)**

1. To estimate progression-free survival at 1-year
2. To correlate blood pressure control and change/discontinuation of antihypertensive medications with tumor responses
3. To correlate symptomatology evaluation by the MD Anderson symptom Inventory (MDASI) with tumor responses
4. To correlate plasma metanephrines and chromogranin A with tumor responses
5. To correlate plasma C-reactive protein and interleukin-6 with symptoms and tumor responses
6. Toxicity assessment by the Common Terminology Criteria for Adverse Events (CTCAE)
7. To correlate both c-MET expression by IHC as well as MET amplification by FISH in archived samples and correlate these biomarkers with overall prognosis and responsiveness to cabozantinib.

**Exploratory Endpoints (For patients with only bone metastases)**

1. Best overall response rate in patients with bone metastases only (8 patients) as determined by FDG-PET/CT
2. FDG-PET/CT $SUV_{max}$, advanced volumetric measures including $SUV_{peak}$, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)
3. Time to skeletal related events
4. Incidence of skeletal related events at 4 months and one year
5. Markers of bone turnover (bone specific alkaline phosphatase and CTx)

## 2.2 Study Design

### 2.2.1 Overview of Study Design

This is a single-arm, open-label phase II study of cabozantinib in subjects with malignant pheochromocytomas and paragangliomas. The primary endpoint is to estimate best overall response rate by RECIST 1.113 in patients with measurable disease determined by a. CT or b. MRI.

The primary objective is to estimate the best overall response rate in patients with measurable disease. Response will include RECIST 1.1 CR, PR, and SD. With 14 patients, the 95% confidence interval for a 45% response rate would be (18.9, 71.1%). For the exploratory objective in the small group of patients with bone metastases, the 95% confidence interval for a 45% response rate with 8 patients would be (10.5, 79.5%). We do not include a formal statistical monitoring rule for toxicity given the established safety profile of this drug.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be tabulated by frequencies and the corresponding percentages. Response rates and their 95% confidence intervals will be estimated. Kaplan Meier survival curves will be used to estimate survival outcomes. Cox proportional hazards regression analysis may be used to assess the association between survival and covariates of interest. The Fisher's exact test or logistic regression analysis will be used for any binary outcomes. T-tests or Wilcoxon rank sum tests will be used to compare continuous variables. Longitudinal models may be explored to study change over time.

Each subject's course will consist of three periods:

- A Pre-Treatment Period in which subjects are consented and undergo screening assessments to be qualified for the study (Section 5.1);
- A Treatment Period in which subjects receive study treatment and undergo study assessments (Section 5.2);

- A Post-Treatment Period in which subjects no longer receive study treatment but undergo follow-up study assessments and contacts (Section 5.3).

### 2.3 Treatment Assignment

It is the responsibility of the investigator to assign a subject number before treating each subject with cabozantinib.

### 2.4 Study Sites

This study will be conducted at one site - The University of Texas MD Anderson Cancer Center.

### 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;
- Specific conditions described in the Management of Adverse Events Sections 3.3.1 and 3.3.1.3;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 4 months 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 $\leq 2$ 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;

- 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) as determined by the investigator unless the patient is deriving clinical benefit as judged by the investigator (case-by-case decision with approval of the Medical Monitor).

# 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) | Disenegrant | 6.0 |
| Colloidal Silicon Dioxide, | Glidant | 0.3 |
| Magnesium Stearate | Lubricant | 0.75 |
| Opadry Yellow Film Coating which includes:<br>- HPMC 2910/Hypromellose 6 cp<br>- Titanium dioxide<br>- Triacetin<br>- 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.

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 signing informed consent through 30 days after the date of the decision to permanently discontinue cabozantinib treatment. Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs should include at minimum confounding factors such as

disease and concomitant medications. 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 detailed in Section 3.3. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.
- The assigned dose for cabozantinib is 60 mg/day. 20 mg 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 Sections 3.3.1 and 3.3.1.3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for AEs may occur at any time per investigator discretion. If treatment is interrupted due to 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.
- Dose interruptions for reason(s) other than AEs (eg, surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Guidelines for the management of specific AEs are provided in Section 3.3.1.3.

**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

### 3.3.1 Management of Adverse Events

Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections (Sections 3.3.1 and 3.3.1.3). Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable if agreed to by the Investigator. All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to the study treatment.

If study treatment of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

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

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

#### 3.3.1.1 Cabozantinib Dose Reinstitution and Reescalation

If the subject recovers from his or her AE and the AE was unrelated to study treatment, then study treatment may be restarted with no change in dose.

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 but no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

#### 3.3.1.2 General Guidelines for Non-Hematologic and Hematologic Adverse Events

**Table 3-3: General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events**

| CTCAE v4.0 | Guidelines/Intervention |
|---|---|
| Grade 1: | Add supportive care as indicated. Continue cabozantinib at the current dose level if the 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 | Interrupt cabozantinib treatment or dose reduction. Add supportive care as indicated.<br>• If cabozantinib dosing is interrupted, then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced |
| Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly | Interrupt cabozantinib treatment and add supportive care as indicated:<br>• For AEs that are easily managed (eg, correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced<br>• For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced |
| Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention | Interrupt cabozantinib treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction. |
| Grade 4 AEs (except easily corrected laboratory abnormalities) | Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and MD Anderson Cancer Center/IND Office, but only with MD Anderson Cancer Center/IND Office approval. |

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

**Table 3-4: General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events**

| CTCAE v4.0 | Intervention |
|---|---|
| **Neutropenia** | |
| • Grade 3 neutropenia with infection requiring IV antibiotic, antifungal, or antiviral intervention<br>• Grade 3 neutropenia ≥ 7 days<br>• Grade 4 neutropenia | Interrupt cabozantinib treatment until resolution to Grade ≤ 1, and resume cabozantinib treatment at a reduced dose. |
| **Thrombocytopenia** | |
| Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia | Interrupt cabozantinib treatment until platelet count is ≥ 100,000/$mm^3$, and resume cabozantinib treatment at a reduced dose. |
| **Febrile Neutropenia** | |
| Grade 3 febrile neutropenia | Interrupt cabozantinib treatment until recovery of ANC to Grade ≤ 1 and temperature to ≤ 38.0°C and resume cabozantinib treatment at a reduced dose. |
| Grade 4 febrile neutropenia | Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and MD Anderson Cancer Center/IND Office but only with MD Anderson Cancer Center/IND Office approval. |
| **Other Grade 4 Hematologic Toxicities** | |
| Grade 4 hematologic toxicities other than anemia | Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and MD Anderson Cancer Center/IND Office, and only with approval by the MD Anderson Cancer Center/IND Office. |
| Grade 4 anemia | Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed in accordance with institutional guidelines. |

| CTCAE v4.0 | Intervention |
|---|---|

ANC, absolute neutrophil count; LLN, lower limit of normal

Neutropenia: Grade 1 (ANC < LLN – 1.5 × $10^9$/L); Grade 2 (ANC <1.5 x $10^9$/L – 1 × $10^9$/L); Grade 3 (ANC <1 × $10^9$/L – 0.5 × $10^9$/L); Grade 4 (ANC <0.5 × $10^9$/L ).

Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).

Thrombocytopenia: Grade 1 (Platelet count <LLN – 75 x $10^9$/L); Grade 2 (Platelet count <75.0 – 50.0 x $10^9$/L); Grade 3 (Platelet count < 50 - 25 × $10^9$/L); Grade 4 (Platelet count < 25 × $10^9$/L).

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#### 3.3.1.3 Cabozantinib Warnings, Precautions, and Guidelines for Management of Specific Adverse Events

The side effect profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea, mucositis/stomatitis), fatigue/asthenia, anorexia, weight loss, skin disorders including palmar-plantar erythrodysesthesia (PPE) syndrome, elevated liver function tests (including alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), osteonecrosis, increased pancreatic enzymes with rare cases of overt pancreatitis, thyroid function disorders, as well as side effects associated with inhibition of vascular endothelial growth factor (VEGF) signaling. The latter of these include arterial and venous thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), transient ischemic attack, and myocardial infarction, hypertension, hemorrhagic events, proteinuria, wound complications, and rare cases of GI perforation, fistulae formation and rectal/perirectal abscess, and reversible posterior leukoencephalopathy (RPLS). Please refer to the Investigator's Brochure for additional details.

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. As of 22 October 2013, in studies with cabozantinib angioedema has been reported to occur in ~0.1% of subjects treated.

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.

Management of diarrhea, nausea and vomiting, stomatitis and mucositis, hepatobiliary disorders (elevated ALT and AST), fatigue, anorexia and weight loss, skin disorders

(PPE and rash), wound healing, hypertension, thromboembolic events, proteinuria, QTc prolongation, hypophosphatemia, thyroid function disorders are presented in this section because these have been observed in previous studies with cabozantinib or represent common class effect toxicity. In addition, guidelines to minimize the risk for potential serious adverse events (SAEs) such as hemorrhagic events, GI and non-GI perforation and fistula formation, wound healing hemorrhagic events, and ONJ are provided in this section.

Please refer to the Investigator's Brochure for additional practice guidelines and management recommendations for side effects potentially related to cabozantinib treatment (such as asymptomatic elevations of amylase and lipase, pancreatitis, rectal and perirectal abscess, cardiac disorders, endocrine disorders, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders); available information on potential risk of congenital, familial and genetic disorders; and guidelines on management of overdose of cabozantinib study treatment.

Below are guidelines for the treatment and/or prevention of certain treatment-emergent AEs of interest that have been associated with, or have a theoretical possibility of occurring with, cabozantinib treatment.

#### 3.3.1.3.1 Gastrointestinal Disorders

The most common GI AEs reported in clinical studies with cabozantinib are diarrhea, oral pain, dyspepsia, stomatitis, and dysphagia.

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 3-2 and Table 3-3.

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

Nausea and Vomiting

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[30,31]. 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 3-2 and Table 3-3.

Stomatitis and Mucositis

Preventive measures include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal 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 (eg, 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.

#### 3.3.1.4 Hepatobiliary Disorders

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

Because subjects may enter the study with elevations of AST/ALT at baseline, the following guidelines in Table 3-5 should be used for dose modifications:

**Table 3-5: Management of Transaminase Elevation**

| Transaminase elevation CTCAE v4.0 | Intervention |
|---|---|
| **Subjects with AST and ALT less than or equal to the ULN at baseline** | |
| **Grade 1** | Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of liver function tests (LFTs). |
| **Grade 2** | Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib |
| **Grade 3** | Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction. |
| **Grade 4** | Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2 to 3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and MD Anderson Cancer Center/IND Office but only with MD Anderson Cancer Center/IND Office approval. |
| **Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (ie, Grade 1) at baseline** | |
| **≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN** | Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib |
| **≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (ie, AST or ALT > 5.0 but ≤ 20.0 x ULN)** | Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib. |
| **Grade 4** | Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2 to 3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and MD A nderson Cancer Center/IND Office , but only with MD Anderson Cancer Center/IND Office approval. |

Cabozantinib treatment should also be interrupted when AST or ALT increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (eg, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × upper limit of normal [ULN], total bilirubin < 1.5 × ULN, aminotransferases ≤ baseline grade).

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

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤ 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be permanently discontinued.

#### 3.3.1.5 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), 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. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure). 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. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. 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.

#### 3.3.1.6 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema 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, 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 3-6.

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 3-6:** Management of Treatment-emergent PPE Syndrome

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

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

#### 3.3.1.7 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.

#### 3.3.1.8 Hypertension

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

Blood pressure should be monitored in a constant position at each visit (either sitting or supine). Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 3-7. 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 week.

**Table 3-7: 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) and < 160 mm Hg<br>**or**<br>> 100 mm Hg (diastolic) and < 110 mm Hg | • Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ;<br>• Maintain dose of cabozantinib;<br>• If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be interrupted and/or reduced. |
| ≥ 160 mm Hg (systolic) and < 180 mm Hg<br>**or**<br>≥ 110 mm Hg (diastolic) and < 120 mm Hg | • Interrupt and/or reduce cabozantinib by one dose level;<br>• Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ;<br>• Monitor subject closely for hypotension;<br>• If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further. |
| ≥ 180 mm Hg (systolic)<br>**or**<br>≥ 120 mm Hg (diastolic ) | • Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications;<br>• Monitor subject closely for hypotension;<br>• When SBP < 150 and DBP < 100, restart cabozantinib treatment at one dose level lower;<br>• If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further. |
| Hypertensive crisis or hypertensive encephalopathy | Discontinue all study treatment |

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

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

### 3.3.1.9 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. Deep vein thrombosis and PE have been observed in clinical studies with

cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (eg, low molecular weight heparin [LMWH]) is established. (Note: Therapeutic anticoagulation with oral anticoagulants, eg, warfarin, or oral platelet inhibitors such as clopidogrel is not allowed in this study). Cabozantinib treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment. During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests in accordance to institutional guidelines. If there are any signs of clinically significant bleedings, cabozantinib treatment should be permanently discontinued.

Arterial thrombotic events (eg, transient ischemic attack, myocardial infarction) have been observed in studies with cabozantinib. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac or thromboembolic events that occurred before initiation of study treatment. Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction or any other clinically relevant arterial thromboembolic complication.

#### 3.3.1.10 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 3-8.

**Table 3-8: Management of Treatment-emergent Proteinuria**

| Severity of Proteinuria (UPCR) | Action To Be Taken |
|---|---|
| ≤ 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) | • No change in cabozantinib treatment required;<br>• Consider confirming with a 24-hour protein assessment within 7 days;<br>• Repeat UPCR within 7 days and once per week. If UPCR < 1 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). |
| ≥ 3.5 mg/mg (≥ 395.9 mg/mmol) | • Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein;<br>• If ≥ 3.5 on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1. |
| Nephrotic syndrome | • Discontinue cabozantinib treatment. |

UPCR, urine protein to creatinine ratio.

#### 3.3.1.11 Corrected QTc Prolongation

The effect of orally administered cabozantinib at 140 mg/day (free-base equivalent) on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled phase 3 study in patients with medullary thyroid carcinoma. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. Accordingly, subjects in this study will be monitored for potential QT effects.

Other factors which may contribute to QTc prolongation include:

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org);

- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels);
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia);
- Medical conditions which can alter electrolyte status eg, severe or prolonged diarrhea.

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

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

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

The MD Anderson Cancer Center/IND Office should be notified immediately of any QTc prolongation event:

- Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated in accordance with standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the MD Anderson Cancer Center/IND Office. If any additional study treatment is given (eg, after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the MD Anderson Cancer Center/IND Office.

#### 3.3.1.12 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Mild hypophosphatemia is usually asymptomatic or symptoms can be non-specific such as weakness, bone pain, rhabdomyolysis, or altered mental status. Other causes of hypophosphatemia such as poor nutrition, chronic alcoholism, malabsorption, excessive antacid use, glucocorticoids use, kidney dysfunction, respiratory alkalosis, vitamin D deficiency 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.

#### 3.3.1.13 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib and other tyrosine kinase inhibitor treatment as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent (Torino et al. 2009). Preliminary data from ongoing studies indicate that treatment-emergent elevation of thyroid stimulating hormone (TSH) by cabozantinib may be dose-dependent in fashion. Hyperthyroidism has also been reported. 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[32].

#### 3.3.1.14 Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as 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, encases, or abuts 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, ulcerative colitis, and other inflammatory GI diseases;
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis;
- History of clinically significant hemoptysis.

Discontinue cabozantinib treatment in subjects who have been diagnosed with a severe bleeding complication.

#### 3.3.1.15 GI Perforation/Fistula and Non-GI Fistula Formation

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

<u>GI perforation/fistula:</u>

- Intra-abdominal tumor/metastases invading GI mucosa;
- Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis;
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess;
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing after abdominal surgery or resolution of

intra-abdominal abscess must be confirmed before initiating treatment with cabozantinib.

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

Non-GI fistula:

Complications from radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation among subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab).

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

#### 3.3.1.16 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of anti-angiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Osteonecrosis has been reported among subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab.

In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing ONJ need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for approximately 4 weeks before a dental procedure and resumed after complete healing has occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the MD Anderson Cancer Center/IND Office on a case-by-case basis.

## 3.4 Concomitant Medications and Therapies

### 3.4.1 Anticancer Therapy

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

### 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 decision to permanently discontinue study treatment are to be recorded in the case report forms.

### 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 (eg, American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);
- Drugs used to control bone loss (eg, bisphosphonates and denosumab) are allowed if started before screening activities and may be initiated or exchanged during the course of the study as clinically indicated, at PI discretion;
- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical;
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion;
    - *Therapeutic doses of LMWH* after the first dose of study treatment are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For

management of thromboembolic complications while on study, refer to section 3.3.1.9.

- Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction);

- For restrictions on oral anticoagulants see Section 3.4.4.

- Antacids, $H_2$ blockers, or proton-pump inhibitors should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib and at least 14 hours before the next dose of cabozantinib, if possible.

Potential drug interactions with cabozantinib are summarized in Section 3.4.5.

### 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 malignant PH and PG;

- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines);

- Any other systemic anticancer treatment (eg, 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*:

-

- Erythropoietic stimulating agents (eg, 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 (Wright 2007);

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. 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 (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

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 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate 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, dexamethasone, 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. 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. Additional details related to these overall conclusions can be found in the investigator brochure.

Additional details regarding potential drug interactions with cabozantinib can be found in 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.

## 4 STUDY POPULATION

### 4.1 Inclusion Criteria

Malignant PH and PG patients will be eligible for enrollment as defined by the inclusion and exclusion criteria as follows:

1. 18 years of age or older
2. Histological confirmation of PH/PG
3. Locally advanced or metastatic disease not amenable to surgery
4. Patients enrolled in the main branch should have measurable disease. Patients with a predominance of bone disease who have small, non-measurable or small measurable lesions other than bone, may be included per the Principal

Investigator's discretion, in the exploratory branch of the study for patients with bone metastases only.

5. Progressive disease per RECIST 1.1 as determined by the investigator within the 12 months preceding study enrollment
6. Assessment of all known disease sites, eg, by computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone scan as appropriate, and/or FDG-PET scan within 28 days before the first dose of cabozantinib
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 .
8. Life expectancy of at least 3 months
9. Organ and marrow function and laboratory values as follows within 4 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. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis
    i. Urine protein/creatinine ratio (UPCR) ≤ 1
    j. Serum phosphorus, calcium, potassium ≥ LLN and magnesium ≥ 1.2 mg/dL
10. Capable of understanding and complying with the protocol requirements and has signed the informed consent document.
11. Sexually active patients (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s).

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

### 4.2 Exclusion Criteria

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

1. Received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 3 weeks, or nitrosoureas/ mitomycin C within 6 weeks before the first dose of study treatment.
2. Prior treatment with cabozantinib
3. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;
4. Received radionuclide treatment (i.e. I $^{131}$ meta-iodo- benzyl guanidine) within 6 months of the first dose of study treatment
5. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment.
6. Receipt of any other type of investigational agent within 28 days before the first dose of study treatment.
7. 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.
8. Prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment.
9. The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
10. The subject requires chronic concomitant treatment of strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).
11. 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 of ≥ 0.5 teaspoon (2.5ml) 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

12. Radiographic evidence of cavitating pulmonary lesion(s)

13. Tumor invading or encasing any major blood vessels

14. 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.

15. Uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders including

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

        ii. Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment

        iii. Any history of congenital long QT syndrome

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

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

cholangitis or appendicitis; patients must be completely recovered from these conditions

- malabsorption syndrome

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

- abdominal fistula
- gastrointestinal perforation
- bowel obstruction or gastric outlet obstruction
- intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more that 6 months before the first dose of study treatment.

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

d. Other clinically significant disorders such as:

i. active infection requiring systemic treatment within 28 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 within 7 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.

16. Unable to swallow tablets

17. A corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before first dose of study treatment. Three ECGs must be performed. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

18. Pregnant or breastfeeding.

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

20. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.
21. Evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment except for cured nonmelanoma skin cancer or cured in situ cervical carcinoma
22. 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, 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 receive their first dose of cabozantinib on this protocol:

1. For patients with measurable visceral metastases CT scans with contrast or MRI are required. Bone scan is required for patients with visceral metastases who also have bone metastases.
2. For patients with only bone metastases FDG-PET/CT scan is the only radiographic test required. FDG-PET/CT assessment will include standard assessment of $SUV_{max}$, as well as advanced volumetric measures including $SUV_{peak}$, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)
3. Laboratory testing (chemistry, hematology tests, interleukin-6, c-reactive protein, thyroid function tests, urine analysis, and thyroid function tests)
4. EKGs will be performed at baseline.
5. Plasma metanephrines and chromogranin A will be obtained at baseline.

6. Evaluation of cancer symptoms by the MD Anderson Symptom Inventory (MDASI) will be obtained at baseline
7. 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 (unless the investigator, with approval of the Medical Monitor, judges the patient is deriving clinical benefit), 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** | **Within 4 days before the first dose of Study Treatment** | **Day 1 of Weeks 3, 5, 7, 9, then every 4 weeks through Week 24, then every 8 weeks (± 5 days); after week 52, every 12 weeks (+/- 5 days)** | **30 - 37 Days after last dose** |
| Informed consent | X | | | |
| Demographics | X | | | |
| Medical and cancer history/demographics | X | | | |
| Physical examination | X | X | X | X |
| Height | X | | | |
| Weight | X | X | X | X |
| Vital signs | X | X | X | X |
| ECOG performance status | X | X | X | X |
| Clinical laboratory tests[1] | X | X | X | X |
| Urinalysis and UPCR | X | X | X | X |
| PT/INR, PTT | X | X | X[2] | |
| TFTs (TSH, free T3, free T4) | X | X | X[2] | |
| 12-lead ECG | X | X | X[2] | X |
| Cabozantinib administration | | | X (daily) | |
| Pregnancy test | X | X | X[2] | X |
| Tumor assessment[3] | X | | X[3] | |
| Bone scan[4] | X | | X[3] | |
| FDG-PET CT[5] | X | | X[3] | |
| Plasma Metanephrines and Chromogranin A[6] | X | | X[3] | |
| Interleukin-6 and c-reactive protein, CTx | X | | X[3] | |
| Concomitant medications | X | X | X | X |
| MDASI[8] | X | X | X (weekly) | X |
| Adverse events | Continuous | | | X |
| Follow-up | | | | X |
| Nurse phone call[7] | | | X (starting after week 24)[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, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total bilirubin, total

protein). CTx will be done, if patient has bone metastases, at screening and every 8 weeks during the first 52 weeks, then every 12 weeks.

[2]Every 4 weeks through Week 24, then every 8 weeks through 52 weeks, then every 12 weeks.

[3]All sites of known disease must be assessed. To occur every 8 weeks during the first 52 weeks, then every 12 weeks.

[4]Patients with both bone and visceral metastases.

[5]Patients with bone metastases only. This is the **only tumor assessment for patients with bone metastases only**.

[6] No additional measurements of plasma metanephrines are needed in patients with normal plasma metanephrines at baseline (Non-functioning PH or PG).

[7] Starting after week 24, nursing phone calls to take place every 8 weeks, at the 4 week period between visits (+/- 5 days). After week 52, phone calls to take place every 12 weeks, at the 6 week period between visits (+/- 5 days). Phone calls will comprise AE and concomitant medication assessments.

[8] MDASI questionnaires will be completed if the patient can be contacted and is willing and able to complete the questionnaire. While patients are encouraged to complete questionnaires at all scheduled time points, patients may refuse to complete a questionnaire at any time.

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 (eg, 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)<br>• hematocrit<br>• platelet count<br>• RBC count<br>• hemoglobin | | |
| **Serum chemistry** | | |
| • albumin<br>• ALP<br>• amylase<br>• ALT<br>• AST<br>• bicarbonate<br>• BUN<br>• chloride | • creatinine<br>• glucose<br>• ionized calcium or total and corrected calcium<br>• lactate dehydrogenase<br>• lipase | • magnesium<br>• phosphorus<br>• potassium<br>• sodium<br>• total bilirubin<br>• total protein |
| **Urinalysis** | | |
| • appearance<br>• color<br>• pH<br>• specific gravity<br>• ketones<br>• protein<br>• UPCR | • glucose<br>• bilirubin<br>• nitrite<br>• creatinine<br>• urobilinogen | • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive) |
| **Other** | | |
| • TSH, Free T3 and T4<br>• Pregnancy text (urine or serum) for women of child-bearing potential | | • PT/INR or PTT<br>• 24 hour urine collection for protein |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate ; GGT, γ-glutamyltransferase; 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.

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 Measurements

Tumor response should be assessed at a frequency of 8 weeks for the first 52 weeks (and then every 12 weeks after that) by CT/MRI and based on RECIST 1.1. In patients with bone metastases, an FDG-PET scan will be obtained every 8 weeks for the first 52 weeks (and then every 12 weeks after that). Subjects continuing to show benefit (complete response [CR], partial response [PR], or stable disease [SD]) may continue on study. Subjects with PD should have their treatment discontinued (unless the investigator, with approval of the Medical Monitor, judges the patient is deriving clinical benefit), and they should enter the post-treatment phase of the study. The same method for tumor assessment should be employed at every assessment.

### 5.6 MDASI

We will use paper or a secure electronic method to collect patient questionnaires when the patient is in the clinic. We will use an interactive voice response (IVR) system, secure web access, or phone calls by field coordinators when patients are away from the clinic. The method of collecting the patient questionnaire assessments will be based on patient preference and may be varied throughout the study based on patient request.

Data collection by IVR. IVR systems are programmed to call patients at home for symptom assessment. The IVR system asks patients to rate each symptom and interference item on the MDASI-Pheo/PGL 0–10 numeric scales using the keypad of a touchtone telephone. Participants electing to use the IVR system may be provided with an informational brochure outlining the steps to complete an IVR call (Appendix G). A telephone number will be provided in the event of questions or problems. Patients will also be given a Patient Identification Number (PIN) for access to the system. IVR calls will be scheduled at a time that is convenient for the patient. Completion or failure of calls will be monitored by the research staff. In the event of missed calls, a notification screen will appear in the IVR system to alert the research staff. The research staff will then contact the patient by telephone, check on their status and, if possible, complete the assessment with the patient during the telephone interview. With the patient's approval, the system then will continue calling the patient at the preset schedule. The IVR symptom and interference data will be available on an MD Anderson intranet site with access

limited to authorized project staff only. Patient data will be identified by subject study number.

Data collection by secure web access. Study questionnaires may be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and was found to be compliant with Health Insurance Portability and Accountability Act (HIPAA), Texas Administrative Codes 202- 203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and MD Anderson Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MD Anderson's Active Directory system. External collaborators are given access to projects once approved by the project sponsor. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. Following publication, study data will be archived in REDCap.

Completion or failure of electronic questionnaire completion will be monitored by the research staff. In the event of missed assessments, the research staff will then contact the patient by telephone, check on their status and, if possible, complete the assessment with the patient during the telephone interview. With the patient’s approval, the system then will continue sending email requests for questionnaire completion to the patient at the preset schedule.

# 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 3.3.

All untoward events that occur after start of study drug through 30 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 events will be documented in the patient's official medical record and in the patient's essential source document. All grades will be recorded in the electronic database (CORe), and the attribution of Not-Related and Related will be assessed.** Assessment of the relationship of the AR to the study treatment by the investigator is based on the following two definitions:

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;

- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (eg, evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

### 6.1.2 Serious Adverse Events

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

**Serious Adverse Event Reporting (SAE) for M. D. Anderson-sponsored IND Protocols:**

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 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 to Supporting Company Exelixis

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.

- Investigator shall notify Exelixis within twenty-four (24) hours of making such discovery by submitting the 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 an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities;

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

    - all SAEs that occur after informed consent 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 (eg, 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 (eg, 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 unexpected adverse drug reactions (unexpected related SAEs) must be reported to the Food and Drug Administration (FDA) as required by 21 CFR 312.32:

- These reports are to be filed utilizing the MD Anderson Cancer Center Internal SAE Report Form for Prompt Reporting;
- The MD Anderson Cancer Center Internal SAE Report Form for Prompt Reporting must be submitted by the study site to Exelixis within one to two business days of submission to the FDA to allow Exelixis time to cross-report to Exelixis' IND. 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 Cancer Center/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

This Phase II study's primary objective is to estimate the best overall response rate in patients with measurable disease. Response will include RECIST 1.1 CR, PR, and SD. With 14 patients, the 95% confidence interval for a 45% response rate would be (18.9, 71.1%). For the exploratory objective in the small group of patients with bone metastases, the 95% confidence interval for a 45% response rate with 8 patients would be (10.5, 79.5%). We do not include a formal statistical monitoring rule for toxicity given the established safety profile of this drug.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be tabulated by frequencies and the corresponding percentages. Response rates and their 95% confidence intervals will be estimated. Kaplan Meier survival curves will be used to estimate survival outcomes. Cox proportional hazards regression analysis may be used to assess the association between survival and covariates of interest. The Fisher's exact test or logistic regression analysis will be used for any binary outcomes. T-tests or Wilcoxon rank sum tests will be used to compare continuous variables. Longitudinal models may be explored to study change over time.

### 7.1 Analysis Population

#### 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 CRFs will be mapped to preferred terms using the National Cancer Institute (NCI) CTCAE v4.0. 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

The sample size will be approximately 22 subjects.

## 8 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).

## 9 ETHICAL ASPECTS

### 9.1 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."

### 9.2 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.

### 9.3 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.

### 9.4 Future Use of Patient Samples

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

## 10 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).

## 11 CONDITIONS FOR TERMINATING THE STUDY

Exelixis and MD Anderson Cancer Center/IND Office 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 MD Anderson Cancer Center/IND Office and the investigator will arrange the procedures on an individual study basis after

review and consultation. In terminating the study, Exelixis and MD Anderson Cancer Center/IND Office and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

## 12 STUDY DOCUMENTATION AND RECORDKEEPING

### 12.1 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 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.

### 12.2 Audits and Inspections

The investigator should understand that source documents for this study should be made available, after appropriate notification, to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

### 12.3 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. PDMS and CORe will be used as the eCRFs for this trial. 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 eCRFs. 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 eCRF entry.

For each subject enrolled, the eCRF must be completed by an authorized delegate from the study staff.

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

## 13 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.

## 14 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, names, and addresses. The investigator should maintain documents not for submission to Exelixis or designees (eg, 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.

## 15 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 (eg, institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined in accordance to guidelines established by the International Committee of Medical Journal Editors.

# 16 REFERENCES


1. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, Habra MA, Rich T, Busaidy N, Cote GJ, Perrier N, Phan A, Patel S, Waguespack S, Jimenez C. J Clin Endocrinol Metab. 2011 Mar;96(3):717-25.

2. Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma. Jimenez C, Rohren E, Habra MA, Rich T, Jimenez P, Ayala-Ramirez M, Baudin E. Curr Oncol Rep. 2013 Aug;15(4):356-71

3. Rationale for anti-angiogenic therapy in pheochromocytoma and paraganglioma. Favier J, Igaz P, Burnichon N, Amar L, Libé R, Badoual C, Tissier F, Bertherat J, Plouin PF, Jeunemaitre X, Gimenez-Roqueplo AP. Endocr Pathol. 2012 Mar;23(1):34-42

4. Bone metastases and skeletal-related events in patients with malignant pheochromocytoma and sympathetic paraganglioma. Ayala-Ramirez M, Palmer JL, Hofmann MC, de la Cruz M, Moon BS, Waguespack SG, Habra MA, Jimenez C. J Clin Endocrinol Metab. 2013 Apr;98(4):1492-7

5. A HIF1alpha regulatory loop links hypoxia and mitochondrial signals in pheochromocytomas. Dahia PL, Ross KN, Wright ME, Hayashida CY, Santagata S, Barontini M, Kung AL, Sanso G, Powers JF, Tischler AS, Hodin R, Heitritter S, Moore F, Dluhy R, Sosa JA, Ocal IT, Benn DE, Marsh DJ, Robinson BG, Schneider K, Garber J, Arum SM, Korbonits M, Grossman A, Pigny P, Toledo SP, Nosé V, Li C, Stiles CD. PLoS Genet. 2005 Jul;1(1):72-80.

6. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, Adams KT, Solis D, Lenders JW, Pacak K. J Clin Oncol. 2007 Jun 1;25(16):2262-9

7. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. Ayala-Ramirez M, Chougnet CN, Habra MA, Palmer JL, Leboulleux S, Cabanillas ME, Caramella C, Anderson P, Al Ghuzlan A, Waguespack SG, Deandreis D, Baudin E, Jimenez C. J Clin Endocrinol Metab. 2012 Nov;97(11):4040-50.

8. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Mol Cancer Ther. 2011 Dec;10(12):2298-308.

9. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Müller T, Ratain MJ, Salgia R. J Clin Oncol. 2011 Jul 1;29(19):2660-6.

10. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. Lee RJ, Saylor PJ, Michaelson MD, Rothenberg SM, Smas ME, Miyamoto DT, Gurski CA, Xie W, Maheswaran S, Haber DA, Goldin JG, Smith MR. Clin Cancer Res. 2013 Jun 1;19(11):3088-94.

11. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. Smith DC, Smith MR, Sweeney C, Elfiky AA, Logothetis C, Corn PG, Vogelzang NJ, Small EJ, Harzstark AL, Gordon MS, Vaishampayan UN, Haas NB, Spira AI, Lara PN Jr, Lin CC, Srinivas S, Sella A, Schöffski P, Scheffold C, Weitzman AL, Hussain M. J Clin Oncol. 2013 Feb 1;31(4):412-9

12. Cabozantinib as a novel therapy for renal cell carcinoma. Vaishampayan U. Curr Oncol Rep. 2013 Apr;15(2):76-82.

13. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. Eur J Cancer. 2009 Jan;45(2):228-47

14. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention.Christensen JG, Burrows J, Salgia R. Cancer Lett. 2005 Jul 8;225(1):1-26. Epub 2004 Nov 11. Review

15. Developing c-MET pathway inhibitors for cancer therapy: progress and challenges.Liu X, Newton RC, Scherle PA. Trends Mol Med. 2010 Jan;16(1):37-45. doi: 0.1016/j.molmed.2009.11.005. Epub 2009 Dec 22. Review.

16. Drug development of MET inhibitors: targeting oncogene addiction and expedience. Comoglio PM, Giordano S, Trusolino L. Nat Rev Drug Discov. 2008 Jun;7(6):504-16. doi: 10.1038/nrd2530. Review.

17. Activating mutations for the met tyrosine kinase receptor in human cancer. Jeffers M, Schmidt L, Nakaigawa N, Webb CP, Weirich G, Kishida T, Zbar B, Vande Woude GF. Proc Natl Acad Sci U S A. 1997 Oct 14;94(21):11445-50.

18. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas.Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z,

Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Lipan J, Slife L, Brauch H, Decker J, Niehans G, Hughson MD, Moch H, Storkel S, Lerman MI, Linehan WM, Zbar B. Nat Genet. 1997 May;16(1):68-73.

19. Met, metastasis, motility and more. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Nat Rev Mol Cell Biol. 2003 Dec;4(12):915-25.
20. Invasive growth: a MET-driven genetic programme for cancer and stem cells. Boccaccio C, Comoglio PM. Nat Rev Cancer. 2006 Aug;6(8):637-45.
21. VEGF receptor protein-tyrosine kinases: structure and regulation. Roskoski R Jr. Biochem Biophys Res Commun. 2008 Oct 24;375(3):287-91.
22. Vascular endothelial growth factors and receptors: anti-angiogenic therapy in the treatment of cancer. Tugues S, Koch S, Gualandi L, Li X, Claesson-Welsh L. Mol Aspects Med. 2011 Apr;32(2):88-111.
23. Angiogenesis and vascular architecture in pheochromocytomas: distinctive traits in malignant tumors. Favier J, Plouin PF, Corvol P, Gasc JM. Am J Pathol. 2002 Oct;161(4):1235-46.
24. Sunitinib induces apoptosis in pheochromocytoma tumor cells by inhibiting VEGFR2/Akt/mTOR/S6K1 pathways through modulation of Bcl-2 and BAD. Saito Y, Tanaka Y, Aita Y, Ishii KA, Ikeda T, Isobe K, Kawakami Y, Shimano H, Hara H, Takekoshi K. Am J Physiol Endocrinol Metab. 2012 Mar 15;302(6):E615-25
25. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Müller T, Ratain MJ, Salgia R. J Clin Oncol. 2011 Jul 1;29(19):2660-6
26. Cabozantinib in progressive medullary thyroid cancer. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. J Clin Oncol. 2013 Oct 10;31(29):3639-46.
27. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. Smith DC, Smith MR, Sweeney C, Elfiky AA, Logothetis C, Corn PG, Vogelzang NJ, Small EJ, Harzstark AL, Gordon MS, Vaishampayan UN, Haas NB, Spira AI, Lara PN Jr, Lin CC, Srinivas S, Sella A, Schöffski P, Scheffold C, Weitzman AL, Hussain M. J Clin Oncol. 2013 Feb 1;31(4):412-9.
28. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Mol Cancer Ther. 2011 Dec;10(12):2298-308.
29. Circulating tumor cells as biomarkers in prostate cancer. Danila DC, Fleisher M, Scher HI.Clin Cancer Res. 2011 Jun 15;17(12):3903-12

30. American Society of Clinical Oncology (ASCO), Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol. 2006;24(18):2932-47. Erratum in: J Clin Oncol. 2006;24(33):5341-2.

31. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010;21 Suppl 5:v232-43.

32. Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol. 2009;6(4):219-28.

## 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