Exelixis Investigator Sponsored CLINICAL STUDY PROTOCOL

An open-label, single-arm, two-stage phase II study investigating cabozantinib in patients with refractory metastatic colorectal cancer

PROTOCOL NUMBER: AGICC 17CRC01/EXELIXIS IST56

STUDY DRUG: Cabozantinib (XL184)

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SPONSOR: Criterium

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SYNOPSIS

TITLE: An open-label, single-arm, two-stage phase 2 study investigating cabozantinib in patients with refractory metastatic colorectal cancer

PROTOCOL NUMBER: 17CRC01

CLINICAL PHASE II

RATIONALE:

Colorectal cancer (CRC) is the third most common cancer diagnosed annually in the United States. Metastatic CRC is the second leading cause of cancer-related death with an estimated 50,000 deaths in the United States and over 500,000 deaths worldwide annually. Despite substantial improvements in treatment over the past decade, metastatic disease remains incurable with a median overall survival of approximately 30 months with optimal combination chemotherapy and biological agents, including anti-VEGF and anti-EGFR antibody therapies. While regorafenib and TAS-102 have been approved for refractory metastatic CRC based on phase III data, these agents are associated with only modest 1-2 month improvements in overall survival when compared to best supportive care. New drug development for metastatic CRC is an urgent priority.

Cabozantinib (XL184) is a potent, orally-bioavailable small-molecule inhibitor of multiple receptor tyrosine kinases, which has demonstrated early evidence of activity in a variety of solid tumors. This agent is currently FDA-approved for treatment of medullary thyroid cancer and renal cell carcinoma. The principal targets of cabozantinib are proteins central to cancer cell growth and tumor angiogenesis: VEGFR2/KDR, MET, RET, AXL, TIE2, and KIT. It is thought that the concurrent inhibition of MET and VEGFR2 underlie the primary activity of cabozantinib seen in solid tumors, differing from the multi-kinase activity of regorafenib, which does not inhibit MET. Based on the theory that dual MET and VEGFR2 inhibition may work synergistically, cabozantinib demonstrated superior survival compared to everolimus in a recently published phase III clinical trial in patients with relapsed/refractory renal cell carcinoma.

Preclinical data has shown that cabozantinib exhibits growth inhibitory and anti-tumor effects in human CRC cell lines as well as in patient-derived tumor xenograft (PDTX) mouse models, respectively. More recently, assessment of treatment effects of cabozantinib versus regorafenib in 10 human CRC tumor explants showed that cabozantinib had greater anti-tumor activity in 9 out of 10 explants. Analysis of tumor growth inhibition index (TGII) demonstrated that cabozantinib was significantly more effective than regorafenib at inhibiting tumor growth (average TGII 3.202 versus 48.48, respectively; $P = 0.007$). Importantly, MET inhibition may be the cause for this difference in efficacy as the HCT116 parental cell line was sensitive to both compounds; however, regorafenib was inactive in the MET kinase active isogenic cell line. These findings suggest that cabozantinib may fill an unmet need by providing a safe and effective treatment once standard of care options are no longer available for patients with metastatic CRC.

We hypothesize that cabozantinib, through dual inhibition of MET and VEGFR2, will lead to improved clinical activity in patients with metastatic CRC refractory to standard of care therapy.

OBJECTIVES

The objectives of this study are:

Primary Objective:

1) To determine the clinical activity of cabozantinib in patients with refractory metastatic CRC using progression free survival (PFS) as primary endpoint.

Secondary Objectives:

1) To determine the response rate (RR) in patients with refractory metastatic CRC treated with cabozantinib.
2) To determine the overall survival (OS) in patients with refractory metastatic CRC treated with cabozantinib.
3) To describe safety and tolerability of cabozantinib in this group of heavily pretreated patients.
4) To retrospectively explore the PFS and RR in patients based on RAS, BRAF, and PIK3CA mutation status.

Exploratory Objectives:

1) Exploratory analysis of predictive and pharmacodynamic markers.

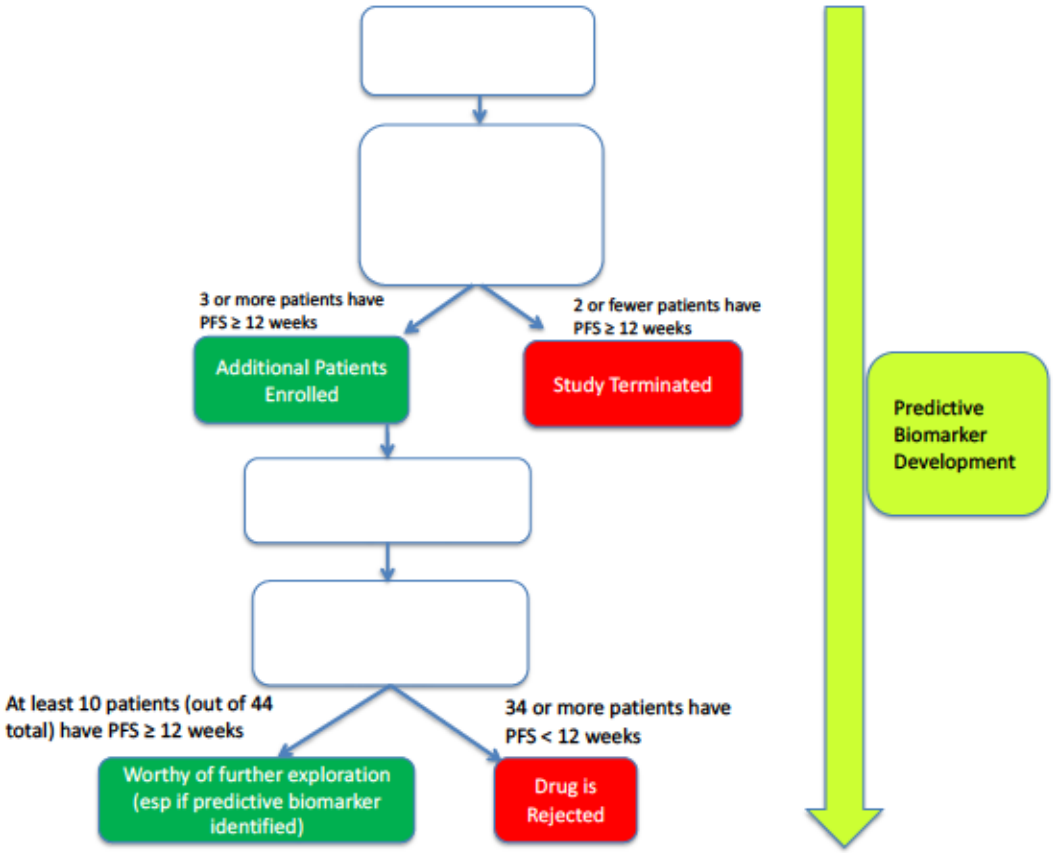
STUDY DESIGN

This is an open-label, single-arm, 2-stage Phase II study of cabozantinib, a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGFR2, RET, AXL, and KIT, in patients with refractory metastatic CRC. Up to 44 evaluable patients will be treated with cabozantinib at a dose of 60 mg daily. One cycle is defined as 21 days.

The primary endpoint is 12-week progression-free survival (PFS). The study will undergo one interim monitoring for futility when 16 evaluable patients have been accrued and dosed, and at least 3 patients have met the 12 week PFS time point. If 2 or fewer patients have a PFS of ≥ 12 weeks, then the study will be terminated. If 3 or more patients have a PFS of ≥ 12 weeks, an additional 28 patients will be enrolled for a total accrual of 44 patients.

Assessment of tumor response will be performed every 6 weeks for the first 12 weeks on study. After 12 weeks, assessment of response will be every 9 weeks. The modified Response Evaluation Criteria in Solid Tumors (RECISTv1.1) will be used to establish disease response or progression.

All patients will be evaluated and graded for adverse events according to the NCI Common Terminology for Adverse Events, version 4.0 (CTCAE).



NUMBER OF SUBJECTS

Approximately 44 subjects will be eligible for this study.

(16 patients in stage 1 + 28 patients in stage 2 = 44 total patients)

TARGET POPULATION

Colorectal cancer patients will be eligible for enrollment as defined by the inclusion and exclusion criteria as follows:

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

1. The subject has a histologic or cytologic diagnosis of colorectal adenocarcinoma that is metastatic or unresectable, and the patient either did not tolerate, is refractory to or progressed (or relapsed) following a fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab; prior epidermal growth factor inhibitor therapy is required for patients with left-sided, RAS wild-type tumors; prior FDA-approved PD-1 inhibitor therapy is required for patients with MSI-H colorectal cancer. Prior regorafenib or TAS-102 treatment is not required;
2. Measurable disease per RECIST 1.1 as determined by the investigator;
3. The subject has had an assessment of all known disease sites e.g., by computerized tomography (CT) scan and/or magnetic resonance imaging (MRI) within 28 days before the first dose of cabozantinib;

4. The subject is ≥ 18 years old on the day of consent;
5. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
6. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy;
7. Adequate archival frozen or fixed tissue available from primary or metastatic site for genotypic analysis (at least 15 unstained slides and/or tumor block);
8. The subject has organ and marrow function and laboratory values as follows within 7 days before the first dose of cabozantinib:
    a. The 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 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) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:
        i. Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);
        ii. Female: Multiply above result by 0.85;
    g. ALT and AST ≤ 3.0 × ULN;
    h. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis;
    i. UPCR ≤ 1;
    j. Serum phosphorus, calcium, magnesium and potassium ≥ LLN.
9. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document;
10. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during 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 or practice abstinence during the study and for 4 months after the last dose of study drug(s);

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

1. The subject has 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. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;

4. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonists may be maintained on these agents;

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

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

7. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test $\geq 1.3 \times$ the laboratory ULN within 7 days before the first dose of study treatment;

8. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel);

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen. ;

9. The subject has experienced any of the following:

   a. clinically-significant GI 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.

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

11. The subject has tumor invading or encasing any major blood vessels;

12. The subject has evidence of clinically significant bleeding from 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;

13. The subject has 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 blood pressure (BP) > 150 mm Hg systolic or > 100 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 transient ischemic attack (TIA), or other ischemic event);
   - myocardial infarction;
   - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (eg, vena cava filter) are not eligible for this study).

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

   i. Active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

   ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,

   Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization

c. Other clinically significant disorders that would preclude safe study participation;

14. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery and/or radiation must have occurred 1 month before the first dose of study treatment. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible;

15. QTcF > 500 msec within 1 month before the first dose of study treatment:

    a. Three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

16. Pregnant or lactating females;
17. Inability to swallow intact tablets;
18. Previously identified allergy or hypersensitivity to components of the study treatment formulations;
19. Diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy;

ESTIMATED LENGTH OF SUBJECT PARTICIPATION

Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. Sponsor or investigator may terminate the study at any time.

ESTIMATED STUDY DATES

First quarter of 2018 to First quarter of 2020 (last study follow-up visit).

INVESTIGATIONAL REGIMEN DOSE/ROUTE/DURATION

Cabozantinib is supplied as 20-mg and administered orally at a dose of 60 mg/day.

SAFETY ASSESSMENTS

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) and urinalysis will be performed every 3 weeks. Other safety evaluations including EKGs will be performed every 6 weeks.

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 by CT or MRI methods at a frequency of every 6 weeks for the first 12 weeks, then every 9 weeks thereafter.

BIOMARKER ASSESSMENTS

Whole blood samples will be obtained pretreatment and +/- 5 days of Cycle 3 Day 1 from consenting patients, which will then be shipped and stored in a repository for future analysis at The University of Arizona. Pending funding availability, archival tumor specimens will be genotyped at The University of Arizona Genetics Core, a CLIA-certified clinical laboratory. Other biomarkers may be evaluated based on ongoing preclinical experiments as well as the scientific literature.

OTHER ASSESSMENTS

Pending funding availability, MET copy number analysis and expression will be assessed by fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC), to explore association with likelihood of response and/or PFS at 12 weeks in patients with metastatic refractory colorectal cancer treated with cabozantinib. Other biomarkers may be evaluated based on ongoing preclinical experiments as well as the scientific literature.

STATISTICAL METHODS

1. Definition of primary outcome/endpoint:
   a) PFS will be defined as the time from administration of the initial dose of cabozantinib to evidence of radiographic progression as defined by RECIST criteria or death from any cause without evidence of disease progression, whichever occurs first.
2. Definition of secondary outcomes/endpoints:
   a) RR is defined using the RECIST 1.1 criteria as the proportion of subjects with a confirmed CR or confirmed PR.
   b) OS will be defined as the time from administration of the initial dose of cabozantinib until death from any cause.
   c) Safety and tolerability analysis of cabozantinib summarized by dose and severity as assessed by the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 and relationship to study drug.
   d) Retrospective analysis of the PFS and RR in patients based on RAS, BRAF, and PIK3CA mutation status through a separate analysis analyzing RR and PFS by RAS, BRAF, and PIK3CA mutation status to those without such mutations.
3. Definition of exploratory outcomes/endpoints:
   a) Exploratory analysis of predictive and pharmacodynamic markers by obtaining pre- and post-treatment whole blood samples pretreatment and +/- 5 days of Cycle 3 Day 1 of treatment for each patient and archived for future studies and analysis.
4. Analytic plan for primary objective:
   a) PFS – each patient will be examined for PFS at 12 weeks and dichotomized as either having progression or not. Using an optimal Simon 2-stage design the first 16 patients will be enrolled and 12-week PFS will be determined. Study enrollment will continue after the 16th patient is accrued and dosed, and at least 3 patients have met the 12 week PFS time point. If 3 or more of these patients have not progressed by 12 weeks, the trial will accrue an additional 28 patients for a total of 44 patients. If 10 or more (total) of these 44 patients are free of progression at 12 weeks, then the Null Hypothesis will be rejected in favor of the alternative suggesting that the treatment has sufficient efficacy to warrant future study.
      i. PFS – Kaplan-Meier estimates of progression-free survival rates will also be calculated along with their corresponding 95% confidence intervals.
5. Analytic plan for secondary objectives:
   a) RR - defined using the RECIST criteria as the proportion of subjects with a confirmed CR or confirmed PR. The point estimate of the RR with a 95% confidence interval based on the exact binomial distribution will be presented.
   b) OS – Kaplan-Meier estimates of progression-free survival rates will be calculated along with their corresponding 95% confidence intervals.
   c) Safety and tolerability analysis - all enrolled patients who receive at least one dose of cabozantinib will have information collected on adverse events, which will be summarized by dose and severity as assessed by the Common Toxicity Criteria for Adverse Events (CTCAE) v. 4.0 and relationship to Study Drug.
   d) Retrospective analysis of the PFS and RR in patients based on RAS, BRAF, and PIK3CA mutation status - point estimates with 95% confidence intervals will be provided for each group, and comparisons will be made using a stratified log-rank test.

6. Analytic plan for exploratory analysis:
   a) Exploratory analysis – peripheral blood collections pretreatment and +/- 5 days of Cycle 3 Day 1 will be obtained and archived for future investigation of predictive and pharmacodynamics biomarkers.
7. Sample size justification:

   From the recent phase III CORRECT trial investigating regorafenib versus best supportive care, the median PFS for patients with refractory colorectal cancer was 1.7 months in the placebo arm. Therefore, the PFS at 12 weeks would be approximately 13%, which will serve as the response rate in the null hypothesis. We have designed the trial to have at least 90% power to detect an improvement in the 12-week PFS rate of at least 20%, therefore the alternative hypothesis is that the 12-week PFS rate is 33%. The optimal design providing at least 90% power to detect the alternative while controlling the type I error rate at 0.05 uses at most 44 patients. This design has an actual type I error rate of 0.0441 (i.e. if the true 12-week PFS rate is less than or equal to 0.13, there is only a 4.4% probability of concluding that the PFS rate is greater than or equal to 0.33). This design has power of 0.906 to detect the alternative hypothesized 12-week PFS rate of 0.33. This trial design uses an average of 25.7 patients.

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AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
BP	blood pressure
BUN	blood urea nitrogen
CHF	congestive heart failure
CrCl	creatinine clearance
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESC	Exelixis Safety Committee
ESMO	European Society of Medical Oncology
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
MTC	medullary thyroid cancer
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PD	progressive disease
PE	pulmonary embolism
PI	principal investigator
PPE	palmar-plantar erythrodysesthesia
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
ONJ	osteonecrosis of the jaw
QTc	corrected QT interval
QTcF	QTc calculated by the Friderica formula
RBC	red blood cell
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SBP	systolic blood pressure
TFT	thyroid function test
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein/urine creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)

1 BACKGROUND AND RATIONALE

1.1 Background:

Colorectal cancer (CRC) is the fourth most common cancer diagnosed each year in the United States, with nearly 135,000 new cases estimated to occur in 2016 (Siegel, 2016). Metastatic CRC is the second leading cause of cancer death, with an estimated 50,000 deaths in the United States and over 500,000 deaths worldwide annually. For advanced disease, FOLFOX (5-fluorouracil (5-FU), leucovorin, oxaliplatin) or FOLFIRI (5-FU, leucovorin, irinotecan) are standard chemotherapy regimens recommended in the first- and second-line treatment settings, alone or in combination with biologic agents targeting either angiogenesis (bevacizumab, ziv-aflibercept, regorafenib) or EGFR (cetuximab or panitumumab). Despite significant improvements with the emergence of these new treatments over the past decade, metastatic disease remains incurable with a median overall survival of approximately 30 months with optimal combination chemotherapy. Primary refractory disease, acquired chemoresistance, and treatment-limiting toxicities leave many otherwise fit patients without a standard treatment option at some point in their disease trajectory. While regorafenib and TAS-102 have been approved for refractory CRC based on randomized phase III data, there was only modest improvement in overall survival seen as compared to best supportive care (Grothey, 2013; Mayer, 2015). New drug development for advanced CRC is an urgent priority.

1.2 Cabozantinib (XL184)

1.2.1 Pharmacology

Cabozantinib is a multi-targeted inhibitor of RTKs. The targets of cabozantinib include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET, VEGFR2 (also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TIE2, TYRO3, and MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely related RTKs KIT and FLT-3. The mode of action for cabozantinib is similar to other drugs targeting RTKs: binding in a fully reversible manner to a region of the kinase domain (including the ATP-binding site) which forces the kinase activation loop into a pseudo-inactive conformation, thereby inhibiting subsequent catalytic activity. The cell-based target inhibition profile of cabozantinib is shown in Table 1-1.

Table 1-1: Inhibition of Key Protein Kinases by Cabozantinib in Cells

Kinase	IC_{50} (nM)
MET	8
VEGFR2/KDR	2[a]
RET (C634W mutant)	85
ROS1 (SLC34A2-ROS1 fusion mutant)	26
KIT	5
FLT-3 (Internal Tandem Duplication mutant)	11
AXL	77
RON	70
MER	4
TIE-2	101

IC_{50}, concentration associated with 50% inhibition; RTK, receptor tyrosine kinase

All assays were performed using cell stimulated by the RTK cognate ligands, except for mutant RTKs and TIE-2 (no exogenous stimulation).

[a] VEGF-mediated ERK phosphorylation.

The IC_{50} values in biochemical kinase assays (Table 1-2) do not always translate evenly in vivo. For example, cabozantinib exhibits comparable potency against MET and VEGFR2 in cellular and in vivo assays, in spite of its apparent greater potency for inhibition of VEGFR2 in biochemical kinase assays.

Table 1-2: Key Protein Kinase Inhibition by Cabozantinib in Biochemical Assays

Kinase	IC_{50} ± SEM (nM)
MET	1.8 ± 0.2
VEGFR2/KDR	0.035 ± 0.007
VEGFR1	12.2 ± 0.7
VEGFR3	6.0 ± 0.6
RET	9.8 ± 2.3
RET-M918T[a]	27 ± 5
ROS1	24
TRKA	64
TRKB	7
FMS/CSF1R	8
AXL	7
MER	0.3
TYRO/RSE/SKY	12
TIE-2	14.3 ± 2.8
FLT-3	14.4 ± 0.8
KIT	4.6 ± 0.5
RON	46

IC_{50}, concentration associated with 50% inhibition; MTC, medullary thyroid cancer; SEM, standard error of the mean.

[a] Most frequent somatic mutation in MTC; associated with poor prognosis (Schilling et al. 2001)

Data from pharmacodynamic experiments have shown that cabozantinib inhibits MET and VEGFR2 in vivo. Oral administration of cabozantinib resulted in blockade of MET phosphorylation in human lung tumor xenografts grown in nude mice, blockade of MET phosphorylation in livers of mice, and blockade of VEGFR2 phosphorylation in mouse lung tissue. For both targets, the duration of action for cabozantinib was sustained, with > 50% inhibition observed for > 8 h post-dose at a single dose level of 100 mg/kg (Yakes et al. 2011). In addition, oral administration of cabozantinib resulted in blockade of phosphorylation of mutationally activated RET in TT human MTC xenografts grown in nude mice (Bentzien et al. 2013).

Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors, with disruption of the vasculature beginning within 24 h after administration, and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and GB (Yakes et al. 2011).

1.2.2 Cabozantinib Nonclinical Toxicology

Toxicity associated with oral administration of cabozantinib was characterized in definitive (GLP-compliant) single-dose and repeat-dose studies in mice, rats, and dogs; a fertility study in rats; embryotoxicity/teratogenicity studies in rats and rabbits; juvenile toxicity studies in rats; in vitro and in vivo genotoxicity bioassays; and an in vitro phototoxicity study. Target tissues for cabozantinib-related toxicity identified in these studies include GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, kidney and skin. Histopathologic changes were also present in bone, central nervous system (CNS) tissues and liver/gall bladder. Adverse findings associated with cabozantinib administration were: (1) generally dose-related; (2) often correlative with clinical signs and/or clinical pathology parameter changes reflective of associated target tissue histopathologic findings; (3) generally reversible upon discontinuation of treatment; and (4) often observed in both rodent and non-rodent species. In definitive reproductive and developmental toxicity studies, cabozantinib reduced fertility in male and female rats, was embryotoxic in rats, produced a fetal soft-tissue malformation (small spleen) in rabbits and produced fetal external malformations (cleft palate/lip, dermal aplasia and kinked or rudimentary tail) in rats. Cabozantinib was negative in in vitro bacterial and mammalian genotoxicity, clastogenicity, and phototoxicity bioassays. The metabolite present at highest plasma concentrations in humans administered cabozantinib, EXEL-1644, was negative in an in vitro bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats dosed subcutaneously with EXEL-1644 for two weeks.

The carcinogenic potential of cabozantinib is being evaluated in an ongoing two-year bioassay in rats. No carcinogenic signal was observed in the rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks.

1.2.3 Clinical Experience

1.2.3.1 Clinical Summary

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs). It is provided as both capsules and tablets, but the two formulations are not interchangeable. Cometriq® (cabozantinib capsules, 140 mg) was approved by the United States Food and Drug Administration (FDA) on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). On 21 March 2014, cabozantinib capsules were approved by the European Commission for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. On 25 April 2016, Cabometyx™ (cabozantinib tablets, 60 mg) was approved by FDA for patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. Cabozantinib is

commercially available as both capsules and tablets in the United States and is currently available only as capsules in the European Union.

The targets of cabozantinib include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET (hepatocyte growth factor [HGF] receptor), vascular endothelial growth factor receptor 2 (VEGFR2, also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely-related RTKs KIT and FLT-3. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis.

Investigator Brochure version 12 (IBv12) includes analysis of 17 clinical studies of cabozantinib for oncology indications including four Phase 1 studies, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 studies (a placebo-controlled study in subjects with MTC, two active-controlled studies in subjects with castration-resistant prostate cancer [CRPC], one ongoing open-label, active-controlled study in subjects with RCC, and one ongoing and enrolling double-blinded placebo-controlled study in subjects with hepatocellular carcinoma [HCC]), one ongoing and enrolling Phase 4 study in MTC, one ongoing maintenance "roll-over" study, and one expanded access study (See Table 5-1 of IBv12). In addition, there are eleven clinical pharmacology studies (See Table 5-2 of IBv12); nine were conducted in healthy subjects alone, one study was conducted that included healthy subjects and subjects with renal impairment, and one study was conducted that included healthy subjects and subjects with hepatic impairment. In addition to these company-sponsored clinical studies, twenty-six investigator-sponsored trials (ISTs) and sixteen National Cancer Institute (NCI)-Cancer Therapy Evaluation Program (CTEP) trials have enrolled subjects in oncology indications.

A pooled analysis of safety data in 2410 subjects with cancer treated with cabozantinib in company-sponsored single-agent studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301, XL184-306, XL184-307, XL184-308, and XL184-401) has been performed. For ongoing studies, serious adverse event (SAE) data are presented through 29 February 2016. Adverse event (AE) data cutoffs are available and shown in Table 5-1 of IBv12.

Cabozantinib is administered as either capsules or tablets. In a bioequivalence study comparing capsules with tablets in healthy adult subjects (Study XL184-010), the geometric mean ratios for both AUC parameters (AUC0-t and AUC0-inf) comparing 140 mg cabozantinib doses of the tablet formulation with the capsule formulation were 108% (90% confidence interval [CI]%: 101, 117). The ratio of geometric means for Cmax (119%; 90% CI%: 107, 132) had a 90% CI

upper bound that slightly exceeds the standard accepted limit of 125%. Therefore, bioequivalence of the cabozantinib capsule and tablet formulations cannot be concluded, and the two formulations are not interchangeable.

The single-agent maximum tolerated dose (MTD) of the capsule in a daily dosing schedule based on 28 days of dosing in Study XL184-001 was determined to be 140 mg. The 140 mg capsule dose level was evaluated in placebo-controlled Phase 3 Study XL184-301 in subjects with MTC. Dose modifications (reductions or interruptions) occurred frequently in the cabozantinib arm of this study. Lower doses of cabozantinib have been explored in other indications. A tablet dose of 60 mg once daily (qd) was evaluated in two Phase 3 studies in prostate cancer, and two ongoing Phase 3 studies, one in RCC and one in HCC, are also evaluating this dose. Ongoing double-blind Study XL184-401 compares the efficacy and safety of cabozantinib 140 mg qd (capsule formulation) with cabozantinib 60 mg qd (tablet formulation). Common to all studies is the titration of the dose to individual patient tolerability.

1.2.3.2 Clinical Safety Profile

A pooled analysis of safety data in 2410 subjects treated with cabozantinib in company-sponsored single-agent studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301, XL184-306, XL184-307, XL184-308, and XL184-401 [blinded comparison of two cabozantinib dose levels]) has been performed. For ongoing studies, SAE data are presented through 29 February 2016. Adverse event data cutoffs for each of the studies are shown in Table 5-1 of IBv12.

Summaries of safety data from Phase 3 studies in RCC (Study XL184-308), MTC (Study XL184-301), and CRPC (Study XL184-307) are also provided in IBv12. All study endpoints have been determined for Studies XL184-301 and XL184-307. Analyses for the primary endpoint and secondary endpoints of Study XL184-308 have been performed; the study is still ongoing and subjects are continuing to receive study treatment. Safety summaries of these three studies are based on data reported in the clinical study reports (CSRs).

Adverse events/and or SAEs are provided for some additional selected studies. These include a Phase 2 study in GB (XL184-201; n = 222), a study conducted in Japanese cancer subjects (XL184-014; n=43), an ongoing double-blind placebo-controlled study in HCC (XL184-309, n=450), three Phase 2 studies evaluating cabozantinib in combination with another drug (XL184-002; n=26, XL184-202; n=77, and XL184-210; n=40), a maintenance "rollover" study (XL184-900; n=37), and twenty-six ISTs (total n=592) and sixteen NCI-CTEP studies (total n=619). SAEs are also provided for company-sponsored clinical pharmacology studies conducted in non-cancer subjects.

1.2.3.2.1 Adverse Events

The AE data summarized in the following sections include those reported and entered in the clinical database as of the dates presented in Table 1-1. For active clinical studies with a "Data Through" date of 29 February 2016, the AE data from the clinical database may not yet include all SAEs. A summary of pooled SAEs from company-sponsored clinical studies with single-agent cabozantinib is provided in Section 5.4.1.4 of the IBv12.

The severity of AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and AE and SAE PTs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 for all studies. For AEs and SAEs, multiple occurrences of the same event in any individual subject are counted once at the highest grade reported. Events that were assessed as possibly related or probably related to cabozantinib are reported as "related," and events that were assessed as not related or unlikely related to cabozantinib are reported as "not related."

Adverse events that occurred in ≥ 10% of the 2410 subjects in the pooled single-agent studies are presented in Table 1-3.

Table 1-3: Summary of Adverse Events Experienced by ≥ 10% of Subjects Treated with Single-Agent Cabozantinib, N = 2410

	All AEs		Related AEs	
MedDRA Preferred Term	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)	Subjects with AE n (%)	Subjects with ≥ Grade 3 AE n (%)
Number of subjects with at least one event	2404 (99.8)	1979 (82.1)	2324 (96.4)	1512 (62.7)
Diarrhoea	1471 (61.0)	251 (10.4)	1300 (53.9)	226 (9.4)
Fatigue	1458 (60.5)	369 (15.3)	1281 (53.2)	312 (12.9)
Nausea	1290 (53.5)	118 (4.9)	1062 (44.1)	89 (3.7)
Decreased appetite	1283 (53.2)	136 (5.6)	1080 (44.8)	104 (4.3)
Vomiting	861 (35.7)	95 (3.9)	612 (25.4)	59 (2.4)
Weight decreased	860 (35.7)	97 (4.0)	671 (27.8)	75 (3.1)
Palmar-plantar erythrodysaesthesia syndrome	835 (34.6)	186 (7.7)	819 (34.0)	185 (7.7)
Constipation	779 (32.3)	31 (1.3)	345 (14.3)	11 (0.5)
Hypertension	708 (29.4)	330 (13.7)	603 (25.0)	284 (11.8)
Dysgeusia	637 (26.4)	2 (0.1)	605 (25.1)	2 (0.1)
Dysphonia	610 (25.3)	5 (0.2)	520 (21.6)	4 (0.2)
Asthenia	557 (23.1)	165 (6.8)	434 (18.0)	124 (5.1)
Dyspnoea	497 (20.6)	76 (3.2)	187 (7.8)	22 (0.9)
Anaemia	479 (19.9)	200 (8.3)	217 (9.0)	70 (2.9)
Stomatitis	474 (19.7)	42 (1.7)	446 (18.5)	41 (1.7)

Abdominal pain	456 (18.9)	95 (3.9)	232 (9.6)	22 (0.9)
Aspartate aminotransferase increased	446 (18.5)	69 (2.9)	382 (15.9)	46 (1.9)
Back pain	444 (18.4)	90 (3.7)	56 (2.3)	6 (0.2)
Mucosal inflammation	444 (18.4)	46 (1.9)	423 (17.6)	44 (1.8)
Pain in extremity	422 (17.5)	53 (2.2)	180 (7.5)	15 (0.6)
Headache	415 (17.2)	30 (1.2)	149 (6.2)	3 (0.1)
Alanine aminotransferase increased	389 (16.1)	74 (3.1)	343 (14.2)	58 (2.4)
Rash	367 (15.2)	15 (0.6)	300 (12.4)	13 (0.5)
Hypothyroidism	359 (14.9)	6 (0.2)	301 (12.5)	3 (0.1)
Cough	354 (14.7)	7 (0.3)	84 (3.5)	1 (0.0)
Oedema peripheral	335 (13.9)	15 (0.6)	101 (4.2)	4 (0.2)
Dizziness	307 (12.7)	12 (0.5)	154 (6.4)	3 (0.1)
Arthralgia	303 (12.6)	30 (1.2)	76 (3.2)	4 (0.2)
Dyspepsia	300 (12.4)	4 (0.2)	224 (9.3)	4 (0.2)
Hypokalaemia	300 (12.4)	90 (3.7)	136 (5.6)	42 (1.7)
Dry mouth	279 (11.6)	0	231 (9.6)	0
Urinary tract infection	269 (11.2)	35 (1.5)	31 (1.3)	3 (0.1)
Dry skin	264 (11.0)	0	219 (9.1)	0
Hypomagnesaemia	262 (10.9)	24 (1.0)	170 (7.1)	17 (0.7)
Dehydration	255 (10.6)	79 (3.3)	139 (5.8)	42 (1.7)
Muscle spasms	255 (10.6)	1 (0.0)	147 (6.1)	1 (0.0)
Hair colour changes	251 (10.4)	2 (0.1)	243 (10.1)	2 (0.1)
Pyrexia	250 (10.4)	16 (0.7)	44 (1.8)	2 (0.1)
Insomnia	244 (10.1)	0	82 (3.4)	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. Adverse events were coded based on MedDRA version 17.0.

Note: This table summarizes pooled data in the clinical database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 cabozantinib arm, XL184-306 cabozantinib arm, XL184-307 cabozantinib arm, XL184-308 cabozantinib arm, and XL184-401).

The most common AEs (≥ 5% incidence) reported at severity of Grade 3 and above were fatigue (15.3%), hypertension (13.7%), diarrhea (10.4%), anemia (8.3%), PPES (7.7%), asthenia (6.8%), pulmonary embolism (6.1%), and decreased appetite (5.6%).

The most frequently (≥ 20% incidence) observed AEs reported as related to cabozantinib, were diarrhea (53.9%), fatigue (53.2%), decreased appetite (44.8%), nausea (44.1%), PPES (34.0%), weight decreased (27.8%), vomiting (25.4%), dysgeusia (25.1%), hypertension (25.0%), and dysphonia (21.6%).

1.2.3.2.2 Serious Adverse Events

The most commonly reported SAEs (≥ 1% incidence) excluding events of disease progression are shown in Table 1-4.

Table 1-4: Summary of Serious Adverse Events Experienced by ≥ 1% of Subjects Treated with Single-Agent Cabozantinib Excluding Events of Disease Progression, N = 2410

	All SAEs		Related SAEs	
MedDRA Preferred Term	Subjects with SAE n (%)	Subjects with ≥ Grade 3 SAE n (%)	Subjects with SAE n (%)	Subjects with ≥ Grade 3 SAE n (%)
Subjects reporting at least one SAE	**1332 (55.3)**	**1221 (50.7)**	**602 (25.0)**	**516 (21.4)**
Pulmonary embolism	120 (5.0)	119 (4.9)	85 (3.5)	84 (3.5)
Vomiting	81 (3.4)	48 (2.0)	40 (1.7)	27 (1.1)
Nausea	72 (3.0)	44 (1.8)	47 (2.0)	31 (1.3)
General physical health deterioration	71 (2.9)	65 (2.7)	13 (0.5)	9 (0.4)
Dehydration	69 (2.9)	54 (2.2)	41 (1.7)	32 (1.3)
Pneumonia	69 (2.9)	58 (2.4)	5 (0.2)	4 (0.2)
Anaemia	59 (2.4)	49 (2.0)	17 (0.7)	13 (0.5)
Abdominal pain	53 (2.2)	43 (1.8)	13 (0.5)	9 (0.4)
Diarrhoea	52 (2.2)	36 (1.5)	42 (1.7)	31 (1.3)
Deep vein thrombosis	46 (1.9)	36 (1.5)	21 (0.9)	16 (0.7)
Fatigue	43 (1.8)	36 (1.5)	27 (1.1)	25 (1.0)
Asthenia	41 (1.7)	30 (1.2)	20 (0.8)	13 (0.5)
Back pain	41 (1.7)	36 (1.5)	1 (0.0)	1 (0.0)
Dyspnoea	39 (1.6)	26 (1.1)	7 (0.3)	5 (0.2)
Pyrexia	36 (1.5)	9 (0.4)	5 (0.2)	2 (0.1)
Urinary tract infection	35 (1.5)	25 (1.0)	4 (0.2)	3 (0.1)
Hyponatraemia	31 (1.3)	29 (1.2)	15 (0.6)	14 (0.6)
Pleural effusion	30 (1.2)	22 (0.9)	6 (0.2)	5 (0.2)
Renal failure acute	30 (1.2)	24 (1.0)	7 (0.3)	5 (0.2)
Convulsion	29 (1.2)	18 (0.7)	5 (0.2)	2 (0.1)
Decreased appetite	28 (1.2)	20 (0.8)	19 (0.8)	14 (0.6)
Bone pain	27 (1.1)	23 (1.0)	0	0
Sepsis	27 (1.1)	27 (1.1)	5 (0.2)	5 (0.2)
Metastatic pain	26 (1.1)	20 (0.8)	1 (0.0)	0
Confusional state	25 (1.0)	17 (0.7)	7 (0.3)	5 (0.2)
Constipation	25 (1.0)	9 (0.4)	9 (0.4)	4 (0.2)
Spinal cord compression	23 (1.0)	22 (0.9)	1 (0.0)	1 (0.0)

MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

Note: Reported SAEs were coded using MedDRA version 17.0. At each level of subject summarization, a subject is counted once if the subject reported one or more events.

Note: This table summarizes pooled data from the safety database for single-agent cabozantinib studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 cabozantinib arm, XL184-306 cabozantinib arm XL184-307 cabozantinib arm, XL184-308 cabozantinib arm, and XL184-401).

Note: Disease progression is expected for subjects with advanced cancer on cabozantinib clinical trials, and as such, events of progression of underlying cancer are not included.

[a] Twenty (20) out of 29 of the observed convulsion events were reported in subjects with glioblastoma (GB) enrolled in Studies XL184-201 or XL184-205. For more information on safety observed in subjects with GB, see Section 5.4.3.1.

1.2.3.2.3 Deaths

Pooled Grade 5 AE data include those reported in subjects with cancer treated with cabozantinib as a single agent on company-sponsored studies (see Section 5.4 for a list of the studies included in this pool). As of 29 February 2016, the incidence of Grade 5 AEs from the pooled single-agent studies was 10.5% (254 subjects). Grade 5 AEs reported in pooled single-agent studies, including events of disease progression, are summarized in Appendix F of the IBv13.

The Grade 5 events that occurred at the highest frequency (≥ 1% incidence) were prostate cancer (2.9%) and general physical health deterioration (1.0%). Per convention, prostate cancer was the PT for disease progression of the cancer under study for Studies XL184- 203 (CRPC cohorts), XL184-306, and XL184-307. Only one event of general physical health deterioration (on Study XL184-307) was assessed as related to study treatment; no events of prostate cancer were assessed as related to study treatment.

Thirty-three (33) of the 254 subjects with Grade 5 AEs had events assessed as related to the study treatment. The only related Grade 5 AEs that occurred more than once were pulmonary embolism (n=4), death (unspecified; n=3), hemorrhage (n=2), respiratory failure (n=2), and sudden death (n=2).

1.2.3.3 Clinical Pharmacokinetics

A PopPK analysis of cabozantinib was performed using data collected from 289 cabozantinib-treated subjects with solid tumors from studies XL184-301 (MTC), XL184-001 (MTC and other tumor types), and XL184-201 (GB) following oral administration of 140-mg capsule daily doses. The predicted effective half-life is approximately 55 h, 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 h. Following oral administration of cabozantinib, Tmax ranged from 2 to 5 h post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold higher 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%). This PopPK 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).

A second PopPK analysis was conducted using plasma concentrations of cabozantinib from 318 subjects with RCC in Study XL184-308 and 63 healthy subjects in Study XL184-020. The RCC subjects received a 60 mg cabozantinib tablet dose qd; a single PK blood sample was taken pre-dose on Day 29 and Day 57 approximately 8 or more hours after the prior evening dose. Dose reductions to daily doses of 40 mg or 20 mg were permitted per protocol. The healthy subjects (n= 21/tablet strength) received a single cabozantinib dose at a tablet strength of 20 mg, 40 mg, or 60 mg; PK blood samples were taken pre-dose and at 20 time points through 504 h post-dose.

Results from this second PopPK analysis indicated that for a White male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (Vz) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h. Inter-individual variability in clearance (percent coefficient of variation [%CV] of CL/F) was estimated to be 46%. Female gender and Asian race were significant covariates on CL/F, where female subjects had 21% lower CL/F compared with male subjects and Asian subjects had 27% lower CL/F compared with White subjects. While the attributes of Asian race and female gender were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. Covariates determined to have a non-significant effect on CL/F were age, baseline body mass index (BMI), baseline hemoglobin, baseline total bilirubin, baseline ALT, baseline serum albumin, baseline calculated creatinine clearance, and population (healthy subjects or subjects with RCC).

The smaller plasma clearance value (2.2 L/h) and longer plasma terminal elimination half-life (99 h) determined in the second (RCC) PopPK analysis, compared to respective values of 4.4 L/h and 55 h estimated in the first (MTC) PopPK analysis was evaluated further. Additional analysis revealed that compared with other cancer patient groups (ie, RCC, CRPC, GB), MTC subjects cleared cabozantinib faster and thus had lower dose-normalized steady-state plasma exposures. Several possible factors may underlie the higher cabozantinib clearance observed in MTC patients in the first PopPK analysis; however, an exact cause has yet to be identified. A PopPK analysis has been performed for another TKI (motesanib) in thyroid cancer patients and showed, similar to cabozantinib, that MTC patients had a higher (67% greater) oral clearance than patients with DTC (Lu et al. 2010). The mechanistic basis for the difference in motesanib CL/F between MTC and DTC patients was also not identified.

In an NCI-CTEP study performed in pediatric subjects with relapsed or refractory solid tumors, including CNS tumors, the mean steady-state AUC0-24 (± standard deviation) at dose levels of 30, 40, and 55 mg/m2/day were 31.9 ± 7.8, 33.3 ± 11.3, and 33.7 ± 15 µg*h/mL, respectively. The average exposure (AUC, Cmax, minimum plasma concentration [Cmin]) values at steady-state across 3 dose groups were in the range of the exposure at steady-state observed for a 140 mg daily dose in adult subjects with medullary thyroid cancer.

Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with

54% in feces and 27% in urine. Results from a PK study of cabozantinib in subjects with renal impairment (XL184-017) indicated that the ratios of geometric LS mean for plasma cabozantinib Cmax and AUCs (AUC0-t and AUC0-inf) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. For subjects with moderate renal impairment, both Cmax and AUCs appeared to be similar when compared to subjects with normal renal function (differences: < 3% and < 7%, respectively). Results from a PK evaluation of cabozantinib in subjects with hepatic impairment (XL184-003) indicated that exposure (AUC0-inf) to cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment, respectively.

A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively, relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose (XL184-004).

Cabozantinib is a substrate of CYP3A4 in vitro. 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 (ie, a < 20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. In healthy subjects, cabozantinib AUC was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole (XL184-007) and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin (XL184-006) in healthy subjects.

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. The IC50 value was 10.1 µM for CYP2B6 and IC50 values were > 20 µM for CYP1A2, CYP2D6, and CYP3A4 isozymes. Cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily dosing for a

minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in subjects with solid tumors (XL184-008).

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Concomitant administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy subjects (XL184-018).

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. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. In addition, cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 has the potential to increase plasma concentrations of cabozantinib.

1.2.3.4 Clinical Activity

Cabozantinib has been studied in a broad selection of tumor types. A summary of the available clinical activity results for cabozantinib in these tumor types is provided in Table 1-5.

Table 1-5: Assessment of Cabozantinib Seen in Multiple Tumor Types

Tumor Type	Study	Median PFS (months)	Week 12 DCR[a] (%)
DTC	XL184-008	not reached	80[b]
RCC	XL184-008	12.9	72[b]
Ovarian Cancer	XL184-203 RDT	5.5	50
	XL184-203 NRE	4.0	NA
CRPC	XL184-203 RDT	6.8	66
	XL184-203 NRE	4.6[c]	NA
	XL184-203 NRE	6.5[d]	NA
HCC	XL184-203 RDT	5.2	66
Breast Cancer	XL184-203 RDT	4.3	47
Melanoma	XL184-203 RDT	2.8	43
NSCLC	XL184-203 RDT	4.0	38
SCLC	XL184-203 RDT	3.4	43
Pancreatic Cancer	XL184-203 RDT	2.7	35
Gastric/GEJ Cancer	XL184-203 RDT	1.4	33
GB	XL184-201	3.7[e]	NA

CRPC, castration-resistant prostate cancer; DCR, disease control rate; DTC, differentiated thyroid cancer; GB, glioblastoma; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; PFS, progression-free survival; NA, not available; NRE, non-randomized expansion; NSCLC, non-small cell lung cancer; RCC; renal cell carcinoma; RDT, randomized discontinuation trial; SCLC, small-cell lung cancer.

Note: Data reported in this table is from the final endpoint analyses.

[a] DCR = (confirmed response [CR] + partial response [PR] + stable disease [1])

[b] DCR at Week 17

[c] For the CRPC cohort that was assigned a dose of 40 mg qd

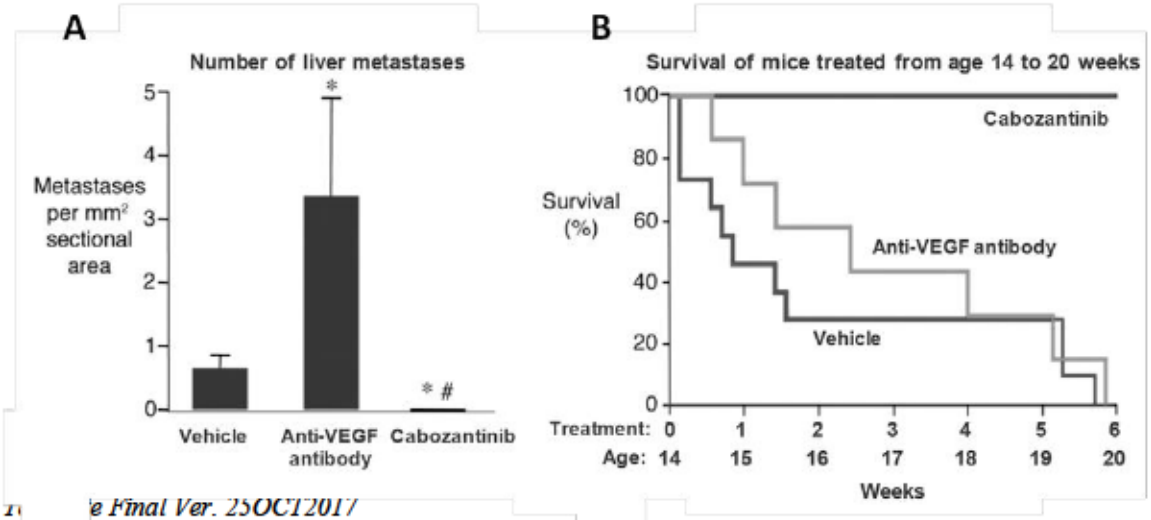
[d] For the CRPC cohort that was assigned a dose of 100 mg qd

[e] For Treatment Group C (100 mg qd). See Section 5.5.2.2 for further details.

1.2.3.5 Translational Medicine

Inhibition of the VEGF signaling pathway alone was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of neuroendocrine pancreatic cancer that spontaneously develops aggressive tumors (Pàez-Ribes et al. 2009). Treatment with cabozantinib for 3 weeks, from age 14 to 17 weeks, significantly prevented formation of liver metastases (Figure 1-1A) in the RIP-Tag2 model compared with anti-VEGF treatment or vehicle alone. The number of liver metastases was 5-fold greater in anti-VEGF antibody-treated animals compared with vehicle-treated animals, and no liver metastases were detected in cabozantinib-treated animals (Figure 4-1A). In addition, treatment with cabozantinib from age 14 to 20 weeks improved survival (Figure 4-1B). Median survival was 14.7 weeks for vehicle-treated animals (n = 12) and 16.4 weeks for anti-VEGF antibody-treated animals (n = 7; $P < 0.05$ vs vehicle), and all cabozantinib-treated animals survived for the full 20 weeks of observation (n = 6; $P < 0.05$ vs vehicle and anti-VEGF antibody; Figure 1-1B).

Figure 1-1: RIP-Tag2 Model: Survival, Cabozantinib versus Vehicle



One of 7 mice in the cabozantinib group that died from a gavage injury at 3.5 weeks was excluded.

* $P < 0.05$ anti-VEGF antibody vs vehicle

# $P < 0.05$ cabozantinib vs anti-VEGF antibody

These results are adapted from Sennino et al. 2012.

These data suggest that dual inhibition of MET and VEGFR2 with cabozantinib leads to potent antitumor efficacy, including protection from metastatic tumor escape, which translates into survival advantages.

1.3 Rationale

1.3.1 Rationale for the Study, Dose, and Schedule

Cabozantinib is a potent, orally bioavailable small-molecule inhibitor of multiple receptor tyrosine kinases which has demonstrated early evidence of activity in a variety of solid tumors. The principal targets of cabozantinib are proteins central to cancer cell growth and tumor angiogenesis: VEGFR2/KDR, MET, RET, and KIT. Cabozantinib is FDA approved for the treatment of progressive metastatic medullary thyroid cancer, where a statistically significant PFS prolongation was demonstrated in the cabozantinib arm compared to placebo [11.2 vs. 4 months; HR 0.28 (95% CI: 0.19, 0.40); p <0.0001]. Cabozantinib also demonstrated a higher response rate as compared to placebo (27% versus 0%; p<0.0001) (Elisei, 2013). Cabozantinib has also been FDA approved for metastatic renal cell carcinoma based on results from the METEOR trial, which showed a significant improvement in median progression free survival with cabozantinib versus everolimus (7.4 months vs 3.8 months, respectively). The rate of progression or death was reduced by 42% with cabozantinib compared to everolimus (HR 0.58; 95% CI, 0.51 to 0.89; P<0.001). The objective response rate was also significantly improved with cabozantinib compared to everolimus (21% vs 5%, respectively; P<0.001).

While mutations in the RET gene underlie much of the efficacy of the drug in medullary thyroid cancer, it is expected that the concurrent inhibition of MET and VEGFR2 may be effective in many solid tumors. In colorectal cancers, MET overexpression was demonstrated in 11/12 human tumor specimens, and demonstrated in vitro that silencing of MET by siRNA led to decreases in colon cancer cell line proliferation, migration, and invasion (Holgren, 2010). In another study of 286 human colorectal cancer specimens, MET overexpression as assessed by immunohistochemistry was seen in 79% (236/286) of specimens. Furthermore, MET overexpression correlated with poor prognosis (De Oliveira, 2009). The proangiogenic ligand, vascular endothelial growth factor (VEGF) binds to at least 3 receptors: VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR4 (FLT4). The VEGF receptors, VEGFR1 and VEGFR2 (KDR) are expressed on the surface of vascular endothelial cells, and on some bone marrow-derived cells. When activated by ligand binding, VEGF receptors mediate endothelial cell invasion, proliferation, and survival. Clinically, inhibition of VEGF by bevacizumab

in combination with IFL yielded improved progression-free survival and overall survival compared to chemotherapy alone in advanced CRC, demonstrating the potential for antiangiogenic approaches to the treatment of cancer (Hurwitz, 2004). There is evidence that MET and VEGFR pathways cooperate to activate downstream effectors regulating tumor growth (Sulpice, 2009; Gerritsen, 2003). Expression of MET is regulated by the same hypoxia-inducible factor system that governs VEGF expression levels. Therefore, both MET and VEGF are induced in response to tumor hypoxia. The downstream mechanisms involved in MET and VEGFR signaling are complex and may vary depending on context; however, inhibition of these targets with single-agent cabozantinib appears to have the potential to shrink tumors. In xenograft animal studies, treatment with cabozantinib resulted in breakdown of tumor endothelium beginning 24 hours after administration, thus suggesting potent anti-angiogenic effects of cabozantinib. This, in turn, led to significant tumor growth inhibition after cabozantinib treatment in multiple tumor models including human medullary thyroid cancer, human breast cancer, human lung carcinoma, and rat glioblastoma (Yakes, 2011). In CRC patient-derived xenograft models, cabozantinib resulted in significantly decreased growth in all tumors, including regression of 2/12 tumors after 28 days of treatment. Treatment with cabozantinib significantly decreased both the number proliferating cells (KI67 expression) and angiogenesis (CD34 staining) when compared to untreated tumors (Atreya, 2013).

While additional laboratory-based testing will be critical to better understand the mechanism of activity of cabozantinib, human testing in the context of a clinical trial is required to determine its efficacy in an unselected CRC population. Based upon the preclinical evidence above suggesting that MET and the VEGF pathway are promising therapeutic targets in colorectal cancers, as well as the preliminary clinical evidence for both anti-tumor efficacy and safety across a broad range of adenocarcinomas, it is appropriate to proceed with a clinical trial of cabozantinib in patients with advanced colorectal cancers. The experience with VEGF-directed therapy with bevacizumab, aflibercept, and regorafenib in the treatment of advanced CRC highlights the importance of angiogenesis in this disease. In addition, a role for MET signaling in CRC is supported by preclinical and clinical data, and by the potential for the close interplay between MET and VEGFR pathways. Furthermore, it is likely that as-yet unrecognized targets in addition to MET and VEGFR contribute to the broad spectrum of anticancer activity demonstrated in the preclinical models.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The objectives of this study are as follows:

Primary Objective:

1) To determine the clinical activity of cabozantinib in patients with refractory metastatic CRC using progression free survival (PFS) as primary endpoint.

Secondary Objectives:

1) To determine the response rate (RR) in patients with refractory metastatic CRC treated with cabozantinib.
2) To determine the overall survival (OS) in patients with refractory metastatic CRC treated with cabozantinib.
3) To describe safety and tolerability of cabozantinib in this group of heavily pretreated patients.
4) To retrospectively explore the PFS and RR in patients based on RAS, BRAF, and PIK3CA mutation status.

Exploratory Objectives:

1) Exploratory analysis of predictive and pharmacodynamic markers.

2.2 Study Design

2.2.1 Overview of Study Design

This is a Phase 2, single-arm, open-label study of cabozantinib in subjects with metastatic colorectal cancer refractory to standard of care options. The primary endpoint is progression-free survival at 12 weeks. A Simon 2-stage optimal design will be used.

2.3 Treatment Assignment

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

2.4 Blinding and randomization

This is an open-label, single-arm study which requires no blinding or randomization.

2.5 Study Sites

This study will be conducted at up to approximately 8 sites.

2.6 Withdrawals

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

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

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue study
- Specific conditions described in the Management of Adverse Events Sections 3.3.2 and 3.3.2.1;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator / Sponsor;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- The minimum dose of study treatment will be 20 mg once daily (qd). Subjects who cannot tolerate 20 mg qd will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

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 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: - HPMC 2910/Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

3.2 Dose, Schedule and Route

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

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 may drink water during this time. 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 their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.

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

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

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

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

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

- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.

- Dose interruptions for reason(s) other than related AEs (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 3.3.2.

Table 3-2: Dose Reductions of Cabozantinib

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

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

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

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

AE, adverse event.

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

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

3.3.1.1 Cabozantinib Dose Reinstitution and Reescalation

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

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

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

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

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

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

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib include anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lipase increased, lactate dehydrogenase (LDH) increased, neutropenia, ALP increased, hyponatremia, and leukopenia. Mild to moderate QTc interval prolongation (10-15ms) has also been observed with a QT interval calculated by the Fridericia formula (QTcF) not exceeding 500 ms.

Subjects may also experience medically important but less frequent adverse events including arterial and venous thrombotic AEs (eg, DVT, pulmonary embolism [PE], transient ischemic attack [TIA], and myocardial infarction [MI]), severe hemorrhagic events, proteinuria, wound healing

complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and reverse posterior leukoencephalopathy syndrome (RPLS).

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

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

The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2 to 3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, because without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.

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

3.3.2.1 Guidelines for Management of Potential Adverse Events

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

- Gastrointestinal disorders (diarrhea, nausea and vomiting, dehydration [prostate cancer studies], stomatitis and mucositis)
- Hepatobiliary disorders (elevated ALT and AST)
- Hematological disorders

- Fatigue, anorexia, and weight loss
- Skin disorders (palmar-plantar erythrodysesthesia syndrome [PPES] and rash)
- Wound healing and surgery
- Hypertension
- Thromboembolic events (venous and arterial)
- Proteinuria
- QTc prolongation
- Hypophosphatemia
- Thyroid function disorders
- Hemorrhagic events
- Osteonecrosis of the jaw (ONJ)
- Angioedema
- Musculoskeletal and connective tissue disorders
- Respiratory, thoracic, and mediastinal disorders

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

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

3.3.2.2 Gastrointestinal Disorders

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

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal

agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 3-4.

Table 3-4: Management of Diarrhea Associated with Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (eg, small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (eg, stool sample for culture) o Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose o Diarrhea not resolving: Start and or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

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

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea

has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Nausea and Vomiting

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

Dehydration may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.

During treatment with cabozantinib good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (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.

3.3.2.3 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more

frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

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

3.3.2.4 Hematological Disorders

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

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

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

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

3.3.2.5 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated in accordance to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see 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. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced per Table 3-2 and Table 3-3.

3.3.2.6 Skin Disorders

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

Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study treatment are presented in Table 3-5.

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 3-5: Management of Treatment-Emergent Hand-Foot Syndrome (PPES)

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

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

[a] Permitted dose levels are defined by individual protocols.

3.3.2.7 Wound Healing and Surgery

VEGFR inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed before starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. If possible, cabozantinib treatment should be stopped for at least 28 days prior to major surgery.

3.3.2.8 Hypertension

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

Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 3-6. Blood pressure should be monitored in a constant position at each visit (either sitting or supine). In general, subjects with known hypertension should be optimally managed before study entry.

Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes after the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

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

Table 3-6: Management of Hypertension Related to Cabozantinib

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

BP, blood pressure.

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

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated blood pressure with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema,

encephalopathy, kidney damage).

3.3.2.9 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. LMWH are the preferred management for thrombotic events, warfarin is not recommended. Cabozantinib treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator/Sponsor. 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, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

3.3.2.10 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Management guidelines are provided in Table 3-7.

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

Table 3-7: Management of Treatment-emergent Proteinuria

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

UPCR, urine protein/creatinine ratio.

3.3.2.11 Corrected QTc Prolongation

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

Unless otherwise specified in certain protocols, only subjects with a baseline QTcF ≤ 500 msec are eligible for cabozantinib research studies. Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or drugs known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

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

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

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

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

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

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

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

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose

3.3.2.12 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Other causes of hypophosphatemia should be ruled out and/or these causes treated in accordance to standard of care. Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements in accordance to standard clinical practice guidelines.

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

3.3.2.13 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib therapy and other tyrosine kinase inhibitors as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent (Torino et al. 2009). Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 3-2 and Table 3-3.

3.3.2.14 Hemorrhagic Events

Hemorrhagic events have been reported with cabozantinib. 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, major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis;
- Underlying medical conditions which affect normal hemostasis (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.

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

Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment, and cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis ($\geq$ 2.5 mL of red blood).

3.3.2.15 GI Perforation/Fistula and Non-GI Fistula Formation

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

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

- Prior GI surgery (particularly when associated with delayed or incomplete healing)

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

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

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

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

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

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

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

3.3.2.16 Osteonecrosis of the Jaw

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

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

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

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

If ONJ occurs, cabozantinib treatment should be held and should not be restarted until the condition has sufficiently healed and the Sponsor has approved the re-initiation of therapy.

3.3.2.17 Angioedema

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

3.3.2.18 Musculoskeletal and Connective Tissue Disorders

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

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

3.3.2.19 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation (Section 0) and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

3.4 Concomitant Medications and Therapies

3.4.1 Anticancer Therapy

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

3.4.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the 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 but may not be initiated or exchanged during the study and require Sponsor approval;
- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice;
- Individualized anticoagulation therapy with heparin 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 low molecular weight heparins (LMWH)* at the time of first dose are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 12 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

- *Therapeutic doses of low molecular weight heparins (LMWH)* after first dose 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 3.3.2.9.

- 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.

- Administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers (Study XL184-018). Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. Cimetidine should be avoided due to potential CYP interactions.

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 colorectal cancer;

- 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:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;

- 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, 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, 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.

Drug interaction tables can be found on the FDA website under "Drug Development and Drug Interactions" and at Indiana University website in "Department of Medicine", "Clinical Pharmacy", "Drug Interactions". The following websites below can be used for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

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

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

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Other Interactions:

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

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

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

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

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

1. The subject has a histologic or cytologic diagnosis of colorectal adenocarcinoma that is metastatic or unresectable, and the patient either did not tolerate, is refractory to or progressed (or relapsed) following a fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab; prior epidermal growth factor inhibitor therapy is required for patients with left-sided, RAS wild-type tumors; prior FDA-approved PD-1 inhibitor therapy is required for patients with MSI-H colorectal cancer. Prior regorafenib or TAS-102 treatment is not required;

2. Measurable disease per RECIST 1.1 as determined by the investigator;

3. The subject has had an assessment of all known disease sites eg, by computerized tomography (CT) scan and/or magnetic resonance imaging (MRI) within 28 days before the first dose of cabozantinib;

4. The subject is $\geq$ 18 years old on the day of consent;

5. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;

6. Recovery to baseline or $\leq$ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy;

7. Adequate archival frozen or fixed tissue available from primary or metastatic site for genotypic analysis (at least 15 unstained slides and/or tumor block);

8. The subject has organ and marrow function and laboratory values as follows within 7 days before the first dose of cabozantinib:

    a. The ANC $\geq 1500/mm^3$ without colony stimulating factor support;

    b. Platelets $\geq 100{,}000/mm^3$;

    c. Hemoglobin ≥ 9 g/dL;

    d. Bilirubin $\leq 1.5 \times$ the ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;

    e. Serum albumin ≥ 2.8 g/dl;

    f. Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:

        iii. Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);

        iv. Female: Multiply above result by 0.85;

    g. ALT and AST $\leq 3.0 \times$ ULN;

    h. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis;

    i. UPCR ≤ 1;

    j. Serum phosphorus, calcium, magnesium and potassium $\geq$ LLN.

9. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document;

10. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during 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 or practice abstinence during the study and for 4 months after the last dose of study drug(s).

4.2 Exclusion Criteria

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

1. The subject has 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. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;

4. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonists may be maintained on these agents;

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

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

7. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test $\geq 1.3 \times$ the laboratory ULN within 7 days before the first dose of study treatment;

8. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel);

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects

without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen;

9. The subject has experienced any of the following:

    a. Clinically-significant GI 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.

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

11. The subject has tumor invading or encasing any major blood vessels;

12. The subject has evidence of clinically significant bleeding from 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;

13. The subject has 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 blood pressure (BP) > 150 mm Hg systolic or > 100 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 transient ischemic attack (TIA), or other ischemic event);
- myocardial infarction;
- thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (eg, vena cava filter) are not eligible for this study).

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

i. Active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,
Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization

c. Other clinically significant disorders that would preclude safe study participation;

14. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery and/or radiation must have occurred 1 month before the first dose of study treatment. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible;

15. QTcF > 500 msec within 1 month before the first dose of study treatment:

a. Three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

16. Pregnant or lactating females;

17. Inability to swallow intact tablets;

18. Previously identified allergy or hypersensitivity to components of the study treatment formulations;

19. Diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy;

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

5.1.1 Demographics

Medical and cancer history, and demographics should be recorded during the pre-treatment period.

5.1.2 Concomitant medications

Concomitant medications will be collected during the pretreatment period and at each study visit.

5.1.3 Vital Signs

Vital signs (body temperature, respiratory rate, blood pressure, and pulse) obtained at each study visit. Blood pressure and pulse will be measured after the subject has been sitting for at least 5 minutes.

When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled time point, and the vitals will be obtained as close to the scheduled blood draw as possible (pre- or post-draw).

5.1.4 Height and weight

Height of subject should be recorded during the pre-treatment period. Weight should be revaluated at each study visit.

5.1.5 Physical Examination

A physical examination will include assessments of ECOG performance status, general appearance, skin, HEENT, thorax/lungs, cardiovascular, abdominal, genitourinary, musculoskeletal, and neurological findings. Any pertinent findings should be documented either in the subject's medical history (if determined to be prior to the first dose of cabozantinib) or as an AE (if new or worsening after the first dose of cabozantinib).

5.1.6 Laboratory Assessment

Local laboratories will perform all laboratory tests, and results will be provided to the Investigator. For a detailed description of the laboratory assessments, please see Section 5.4. Blood and urine samples for hematology, serum chemistry, coagulation panel, TFTs, CEA and urinalysis and urine protein/urine creatinine ration (UPCR) will be prepared using standard procedures and analyzed during the pretreatment period. Laboratory results will be reviewed by the Investigator for clinical significance.

5.1.7 Pregnancy test

A pregnancy test (urine or serum) will be collected during pretreatment period and within 7 days of study treatment start. It will be repeated every Odd Cycle if female patient of child-bearing potential remains on study.

5.1.8 Electrocardiogram (ECG)

ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures. Pre-treatment ECGs should be performed after vital signs are

obtained and before any blood draws. Abnormalities in the ECG that lead to a change in subject management (e.g., dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs). When an ECG time point coincides with other activities, the ECG will be collected first, followed by vital signs.

5.1.9 Archival tumor tissue (optional)

Adequate archival frozen or fixed tissue available from primary or metastatic site for genotypic analysis (at least 15 unstained slides and/or tumor block).

5.1.10 Whole blood collection (optional)

Whole blood will be collected and banked for future correlative/exploratory analysis and will be obtained Cycle 1 Day 1 (-7 day window) and again +/- 5 days of Cycle 3 Day 1.

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

5.2 Treatment Period

During the Treatment Period subjects will receive cabozantinib until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 2.6. 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 1 Cycle = 21 days			Post-Treatment Period
	Within 28 days before 1st Dose of Study Treatment	Cycle 1 Day 1 (-7 day window)	Day 1 of each subsequent Cycle (± 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
Hematology (CBC w diff and platelets	X	X	X	X
Chemistry (CMP, magnesium, LDH, phosphorus	X	X	X	X
Amylase/Lipase	X	X	X	X
GGT		X		
Urinalysis and UPCR	X		X	X
PT/INR, PTT	X		X[1]	
TFTs (TSH, free T3, free T4)	X		X[1]	
12-lead ECG	X[2]		X[1]	X
Cabozantinib administration		X (daily)	X (daily)	
Pregnancy test	X	X	X[1]	X
Tumor assessment[3]	X		X (every 6 weeks for first 12 weeks, then every 9 weeks)	
CEA	X		X (every 3 weeks)	
Archival tumor tissue	X[3]			
Whole blood collection for correlative analysis		X[4]	(Cycle 3 Day 1)[4]	
Concomitant medications	X		X	X
Adverse events	Continuous			X
Interim analysis			X[5]	
Follow-up/EOS				X[6]

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; EOS end-of-study

[1]Odd cycle assessments

[2]ECG done in triplicate to assess average QTc for screening

[3]All sites of known disease must be assessed

[4]Adequate archival frozen or fixed tissue available from primary or metastatic site for genotypic analysis (at least 15 unstained slides and/or tumor block). Whole blood for correlative/exploratory analysis will be obtained Cycle 1 Day 1 (-7 day window) and Cycle 3 Day 1 (+/- 5 days)

[5]Upon enrolling the 16th patient, an interim analysis will be performed to evaluate PFS once 3 patients have met the 12 week PFS mark. An additional safety DMSC review will occur once 16 patients have been dosed through 12 weeks.

[6]Patients will be followed for up to 12 months to record their health and disease status after EOS assessment

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

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

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

5.3 Post-Treatment Period

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

Additional follow-up to record health and disease status will be done for up to 12 months after EOS. Survival information can be collected via telephone and should occur every 90 days (+/- 30 days) up to 12 months after EOS.

5.4 Laboratory Assessments

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hematocrit • platelet count • RBC count • hemoglobin		
Serum chemistry		
• albumin • ALP • amylase • ALT • AST • bicarbonate • BUN • chloride	• creatinine • GGT (day 1 only) • glucose (non-fasting permitted) • ionized calcium or total and corrected calcium • lactate dehydrogenase • lipase	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Other		
• TSH, Free T3 and T4 • Pregnancy test (urine or serum) for women of child-bearing potential		• PT/INR or PTT • 24-hour urine collection for protein

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; 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 Assessment

For the purposes of this study, participants should be re-evaluated for response every 6 weeks for the first 12 weeks, followed by every 9 weeks thereafter.

Response and progression will be evaluated in this study using the new international criteria proposed by the RECISTv1.1 guideline [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

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

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond

the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions based on FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing based on the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner like a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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

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

5.5.1 Response Criteria

5.5.1.1 Evaluation of Target Lesions

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

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

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

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

5.5.1.2 Evaluation of Non-Target Lesions

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

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

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

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

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

5.5.1.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

5.5.1.4 Evaluation of Best Overall Response

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

Table 5-2: Participants with Measurable Disease (Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note:	Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 5-3: Participants with Non-Measurable Disease (Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
*	'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised	

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 trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the 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 this protocol. All untoward events that occur from time of first study drug dose through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits and includes the new onset of or increase in pain during this period.

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.

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

- Result in death;
- Is life-threatening (i.e., in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.
- Results in persistent or significant disability or incapacity:
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):

- Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

6.1.3 Relationship to Study Treatment

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

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause 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 (e.g., evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

6.1.4 Serious Adverse Event Reporting

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures, from the time of first study drug dose, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs that are assessed by the PI as **related** to drug or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

6.1.5 Regulatory Reporting

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;

- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.

- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.

- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The PI shall provide a

copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.

- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

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 of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

6.2.2 Pregnancy/Lactation Exposure

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. Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms 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. 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 overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

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

7 STATISTICAL CONSIDERATIONS

7.1 Analysis Population

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 Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v4.0. Listings of AEs will be provided.

7.3 Sample Size

The stage I sample size will consist of 16 subjects for interim analysis, then an additional 28 subjects for stage II for a total of 44 subjects.

7.3.1 Sample Size Justification

Based on the phase III CORRECT trial investigating regorafenib versus best supportive care, the median PFS for patients with refractory colorectal cancer was 1.7 months in the placebo arm. Therefore, the PFS at 12 weeks would be approximately 13%, which will serve as the response rate in the null hypothesis. We have designed the trial to have at least 90% power to detect an improvement in the 12-week PFS rate of at least 20%, therefore the alternative hypothesis is that the 12-week PFS rate is 33%. The optimal design providing at least 90% power to detect the alternative while controlling the type I error rate at 0.05 uses at most 44 patients. This design has an actual type I error rate of 0.0441 (i.e. if the true 12-week PFS rate is less than or equal to 0.13, there is only a 4.4% probability of concluding that the PFS rate is greater than or equal to 0.33). This design has power of 0.906 to detect the alternative hypothesized 12-week PFS rate of 0.33. This trial design uses an average of 25.7 patients.

8 OTHER ANALYSES

8.1 Analytic Plan Primary, Secondary, and Exploratory Endpoints

8.1.1 Primary Endpoint:

Progression-free survival will be defined as the time from administration of the initial dose of cabozantinib to evidence of radiographic progression as defined by RECIST criteria or death from any cause without evidence of disease progression, whichever occurs first. Each patient will be examined for PFS at 12 weeks and dichotomized as either having progression or not. Using an optimal Simon 2-stage design, the first 16 patients will be enrolled and 12-week PFS will be determined. If 3 or more of these patients have not progressed by 12 weeks, the trial will accrue an additional 28 patients for a total of 44 patients. If 10 or more (total) of these 44 patients are free of progression at 12 weeks then the Null Hypothesis will be rejected in favor of the alternative suggesting that the treatment has sufficient efficacy to warrant future study.

Kaplan-Meier estimates of PFS rates will be calculated along with their corresponding 95% confidence intervals.

Evaluable for Response

Only those participants who have received at least 2 cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. Note: Participants who exhibit objective disease progression or die prior to Cycle 3 will also be considered evaluable. Participants who do not meet the criteria for being evaluable for response defined above may be replaced to reach the sample size necessary for interim analysis.

8.1.2 Secondary Endpoints:

8.1.2.1 Response Rate (RR)

Response rate is defined using the RECISTv1.1 criteria as the proportion of subjects with a confirmed CR or confirmed PR. The point estimate of the RR with a 95% confidence interval based on the exact binomial distribution will be evaluated.

8.1.2.2 Overall Survival (OS)

Overall survival will be defined as the time from administration of the initial dose of cabozantinib until death from any cause. PFS is defined above. Kaplan-Meier estimates of overall survival and progression-free survival rates will be calculated along with their corresponding 95% confidence interval.

8.1.2.3 Tolerability and Safety

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

8.1.2.4 PFS and RR Based on Molecular Status

Analysis of the PFS and RR in patients based on RAS, BRAF, and PIK3CA mutation status will be done with point estimates of 95% confidence intervals provided for each group, and comparisons will be made using a stratified log-rank test. Other biomarkers may be evaluated based on ongoing preclinical experiments as well as the scientific literature.

8.1.3 Exploratory Endpoint

8.1.3.1 Biomarker Analysis

Exploratory analysis of predictive and pharmacodynamic biomarkers will be performed by collecting pre- and post-treatment peripheral blood collection during pretreatment period and again on Cycle 3 Day 1 +/- 5 days. Samples will be archived for future investigation. See Appendix C for list of biomarkers.

8.2 Biomarker, Correlative, and Special Studies

8.2.1 Laboratory Correlative Studies

Whole blood samples will be obtained at Cycle 1 Day 1 (-7 day window) and on Cycle 3 Day 1 (+/- 5 days) from consenting patients, which will then be shipped and stored in a repository for future analysis at The University of Arizona. Pending funding availability, archival tumor specimens will be genotyped at The University of Arizona Genetics Core, a CLIA-certified clinical laboratory. Other biomarkers may be evaluated based on ongoing preclinical experiments as well as the scientific literature.

8.2.2 Archival Tumor Tissue

Pending funding availability, MET copy number analysis and expression will be assessed by fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC), to explore association with likelihood of response and/or PFS at 12 weeks in patients with metastatic refractory colorectal cancer treated with cabozantinib. Other biomarkers may be evaluated based on ongoing preclinical experiments as well as the scientific literature.

8.2.3 Whole Blood

Potential candidate markers for future study include soluble members of the MET/HGF and VEGF pathways (Please see Appendix C).

9 DATA SAFETY MONITORING

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all of the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's six month DSM report.

The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six month report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

Quality Control and Quality Assurance

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

10 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and crosscheck of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator.

11 MULTICENTER GUIDELINES AND STUDY COMMITTEES

This protocol will adhere to the policies and requirements of the AGICC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor, Coordinating Center, and Participating Institutions are listed below.

- The Sponsor/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12 ETHICAL ASPECTS

12.1 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."

12.2 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.

12.3 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.

12.4 Future Use of Patient Samples

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

13 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications may be made and will be prepared, reviewed, and approved by representatives of the investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

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).

14 CONDITIONS FOR TERMINATING THE STUDY

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

15 STUDY DOCUMENTATION AND RECORDKEEPING

15.1 Investigator's Files and Retention of Documents

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

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

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray,

pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

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

If the investigator cannot guarantee the archiving requirement at the study site for any or all the documents, special arrangements must be made between the investigator and Exelixis to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

15.2 Source Documents and Background Data

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

15.3 Audits and Inspections

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

15.4 Case Report Forms

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to CRFs. Additional

procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

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

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

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

16 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 during these monitoring visits are resolved.

17 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 storage and central review. Exelixis may access data and/or receive data transfer upon study completion.

18 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 Exelixis with a copy of any proposed publication

or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts 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.

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Appendix A: Performance Status Criteria

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

ECOG, Eastern Cooperative Oncology Group

1. Kwong LN, Costello JC, Liu H, Jiang S, Helms TL, Langsdorf AE, Jakubosky D, Genovese G, Muller FL, Jeong JH *et al*: **Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma**. *Nature medicine* 2012, **18**(10):1503-1510.

Protocol #:
Study Participant Drug Diary

Cabozantinib Drug Tablets

Directions for Use

Immediately call your doctor if you have any questions about taking the tablets or about any reactions or side effects.

Directions

DO

- Take the tablet on an empty stomach with a full glass of water (8 ounces).
- Take the tablets at approximately the same time each dosing day.

DO NOT

- **DO NOT** eat 2 hours before and 1 hour after each dose (except for water).
- **DO NOT** make up missed doses.
- **DO NOT** make up vomited doses.

Storage of Drug

Cabozantinib should be stored at controlled room temperature (20°C to 25°C, 68°F to 77°F). Do not refrigerate or freeze. Keep away from cold or heat sources.

Protocol: **Participant Name:**
Study Drug: Cabozantinib **Participant MRN:**

Study Drug Instructions

How Much: ☐ 60mg ☐40mg ☐20mg
How Often: Once daily

- For additional dosing instructions, see "Directions for Use" sheet
- Please call with any questions:
  _____

Dosing Log: Cycle # ____ Week # ____ Day # ____

	Date	Time of Dose	Amount Taken	Comments
Ex:	6/1/2012	8 am	1 pill / 60mg	Vomited pill
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				

Name of person completing this form: _____

Signature of person completing this form: _____

Date: _____

Appendix C: Exploratory biomarkers

Predictive and pharmacodynamics biomarker analysis may include but not limited to the following:

HGF
MET
Autophagy markers (LC3 and SQSTM1/p62)
VEGF
VEGFR-2
AKT
PD-L1
cfDNA and cfRNA
Epigenetic hypermethylation/modifications