TITLE: Open Label Phase II Trial of Cabozantinib in Patients with Metastatic Castrate Resistant Prostate Cancer (mCRPC) and Known Amplifications or Activating Mutations in Gene Targets of Cabozantinib or Liver Metastases who have Received Prior Anti-Androgen Therapy

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Principal Investigator: David M. Nanus, M.D.
525 E 70th St, Starr 341
New York, NY 10065
646−962−2084
dnanus@med.cornell.edu

Co-Investigators:

Columbia University Medical Center
Mark Stein, M.D., Division of Hematology & Medical Oncology

University of Pittsburgh Medical Center
Leonard Appleman, M.D., Ph.D., Division of Hematology & Medical Oncology

Karmanos Cancer Institute
Elisabeth Heath, M.D., Division of Hematology & Medical Oncology

Dana Farber Cancer Institute (Correlatives Only)
Himisha Beltran, M.D., Division of Hematology & Medical Oncology

Statistician:
Zhengming Chen
1300 York Avenue New
York, NY 10065
zhc2006@med.cornell.edu

Participating Sites:

Weill Cornell Medicine
David M. Nanus, M.D.
525 E 68th St, Starr 341
New York, NY 10065
646−962−2084
dnanus@med.cornell.edu

Columbia University Medical Center
Mark N. Stein, M.D.
161 Fort Washington Ave
New York, NY 10032
212-305-5874
mns2146@cumc.columbia.edu

University of Pittsburgh Medical Center
Leonard Appleman, M.D., Ph.D.
5115 Centre Ave.
Pittsburgh, PA 15232
412-692-4724
applemanlj@upmc.edu

Karmanos Cancer Institute
Elisabeth Heath, M.D.
4100 John R, HW04H0
Detroit, MI 48201
313-576-8734
heathe@karmanos.org

Dana Farber Cancer Institute (Correlatives Only)
Himisha Beltran, M.D.
450 Brookline Ave.
Boston, MA 02215-5450
617-632-2429
himisha_beltran@dfci.harvard.edu

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

Weill Cornell Medical

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Institution Name

David M. Nanus M.D

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Principal Investigator's Name Principal Investigator's Signature

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Date

LIST OF ABBREVIATIONS

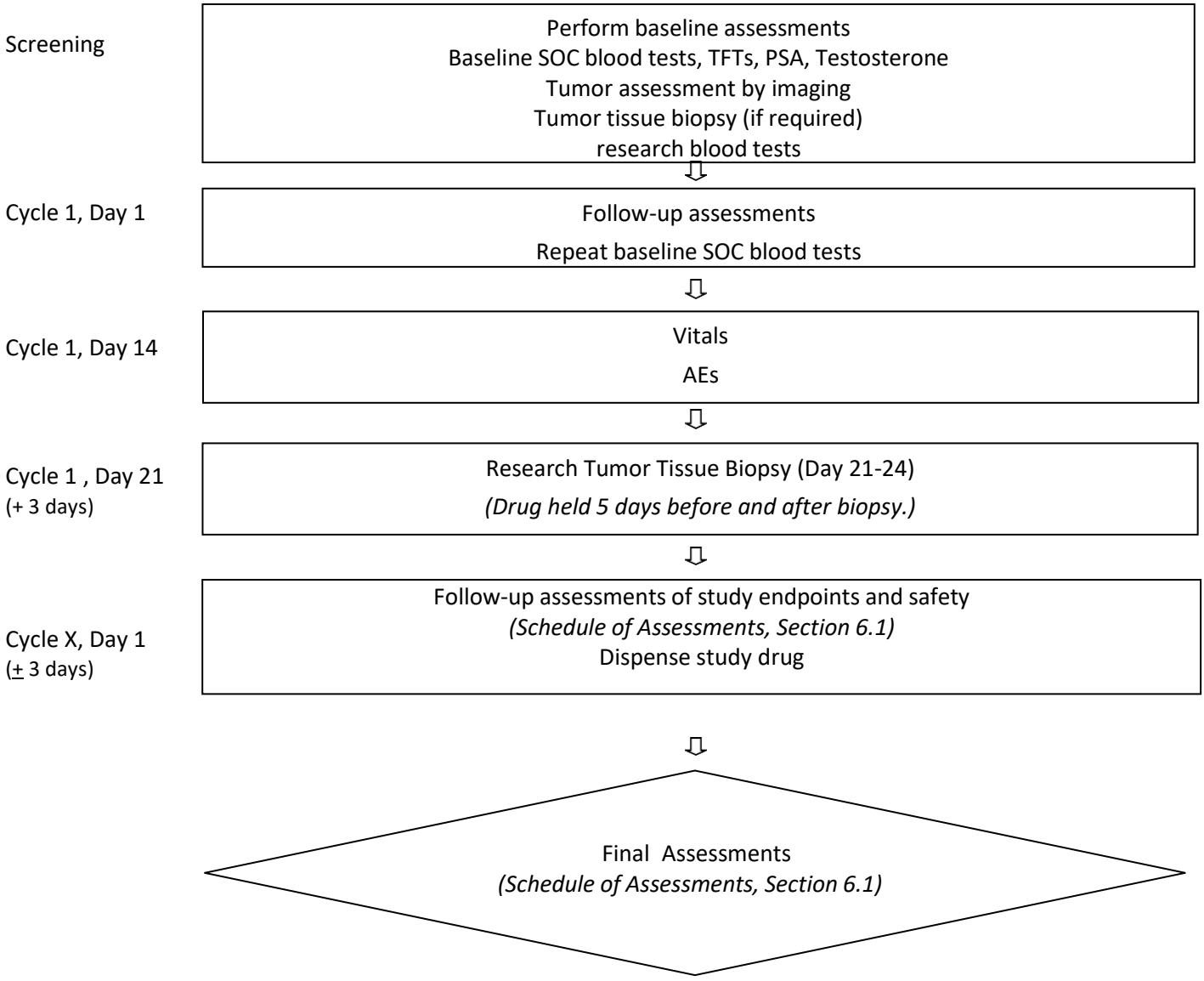
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AR	Androgen Receptor
CFR	Code of Federal Regulations
CrCl	Creatinine clearance
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PCWG3	Prostate cancer working group 3
PFS	Progression-free survival
PHI	Protected Health Information
PI	Principal Investigator
PO	*Per os* (by mouth)
RECIST	Response Evaluation Criteria In Solid Tumors
REDCap	Research Electronic Data Capture
rPFS	Radiographic progression-free survival
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

1. PROTOCOL SUMMARY

Full Title	Open Label Phase II Trial of Cabozantinib in Patients with Metastatic Castrate Resistant Prostate Cancer (mCRPC) and Known Amplifications or Activating Mutations in Gene Targets of Cabozantinib or Liver Metastases who have Received Prior Anti-Androgen Therapy
Short Title	Cabozantinib for mCRPC
Clinical Phase	Phase 2
Principal Investigator	David Nanus, MD
Sample Size	N = 30
Accrual Ceiling	Enroll up to 30 subjects and screen up to 100 subjects
Study Population	Men with CRPC who have progressed on a second-line anti-androgen therapy
Accrual Period	24 months
Study Design	This is a phase II non-randomized, open label trial designed to evaluate treatment response and survival of patients with mCRPC who harbor evidence of increased signaling (via evidence of DNA amplification or RNA overexpression) of the targets of cabozantinib (MET, KIT, RET, VEGFR-1 (FLT1), VEGFR-2 (KDR), VEGFR-3 (FLT4), FLT3, AXL, TRKB, and TIE2) or who have or liver metastases. All patients will receive cabozantinib at 40 mg/day. Dose reduction (from 40 to 20 mg and to 20 mg every other day) or interruptions of treatment will be allowed for unacceptable adverse events (AEs).
Study Duration	Approximately 12 months after enrollment, then patients will shift to long−term follow up
Study Agent	Cabozantinib, 40 mg PO daily
Primary Objective	To assess the radiographic response proportion of cabozantinib in patients with metastatic CRPC who have progressed on an androgen receptor signalinginhibitor whose tumor possess a molecular abnormality that is targeted by cabozantinib or who have liver metastases
Secondary Objectives	• To assess PSA decline by PCWG3 • To measure overall survival (OS)
Exploratory Objectives	• To explore prognostic and/or predictive biomarkers of cabozantinib in whole blood, plasma and tumor samples: o To evaluate for and measure changes in targeted genes found in cell-free DNA at baseline, in response to treatment, and at the time of disease progression o To explore the effects of cabozantinib on

	tumor immune microenvironment response through on-treatment biopsy, ideally of same pre-treatment site, and collection of plasma for analysis ○ To explore any relationship between baseline and on-treatment tumor genomic alterations (such as mutations, translocations, messenger ribonucleic acid [mRNA], protein expression and localization) with anyobserved antitumor activity
Endpoints	Radiographic progression free survival, response rate (radiographic RR, ≥50% PSA response rate, overall survival, and adverse event rate

1.1 Schema


Screening
Perform baseline assessments
Baseline SOC blood tests, TFTs, PSA, Testosterone
Tumor assessment by imaging
Tumor tissue biopsy (if required)
research blood tests
Cycle 1, Day 1
Follow-up assessments
Repeat baseline SOC blood tests
Cycle 1, Day 14
Vitals
AEs
Cycle 1 , Day 21
(+ 3 days)
Research Tumor Tissue Biopsy (Day 21-24)
(Drug held 5 days before and after biopsy.)
Cycle X, Day 1
(± 3 days)
Follow-up assessments of study endpoints and safety
(Schedule of Assessments, Section 6.1)
Dispense study drug
Final Assessments
(Schedule of Assessments, Section 6.1)

1.2 Study Objectives

To determine the anti-tumor effects of cabozantinib in patients with mCRPC who have received prioranti-androgen therapy and harbor known amplifications or activating mutations in gene targets of cabozantinib or who have liver metastases.

1.2.1 Primary Objectives

To assess the radiographic response proportion of cabozantinib in patients with metastatic CRPC who have progressed on an androgen receptor signaling inhibitor whose tumor possess a molecular abnormality that is targeted by cabozantinib or who have liver metastases.

1.2.2 Secondary Objectives

- To assess PSA decline by PCWG3 criteria
- To measure overall survival (OS)

1.2.3 Exploratory Objectives

- To evaluate for and measure changes in targeted altered genes found in cell free DNA at baseline, inresponse to treatment, and at the time of disease progression.
- To explore the effects of cabozantinib on tumor immune microenvironment response through on-treatment biopsy and collection of plasma for analysis.
- To explore any relationship between baseline and on-treatment tumor genomic abnormalities (suchas mutations, translocations, messenger ribonucleic acid [mRNA], protein expression and localization) with any observed antitumor activity.

2. BACKGROUND

2.1 Prostate Cancer

Prostate cancer (PC) is the most common non-skin cancer diagnosed in men in the United States and the second most common cause of cancer-related mortality [1]. Despite advances in diagnostic technology and treatment strategies, up to 40% of patients treated with primary therapy with curative intent will experience disease progression [2]. The standard of care for men who develop metastatic PC has evolved over the past few years. Results of three phase III studies, CHAARTED, STAMPEDE and LATITUDE, have shown that men with newly diagnosed metastatic PC benefit from early use of docetaxel chemotherapy or abiraterone acetate plus prednisone in conjunction with androgen deprivation therapy (ADT)[3-6]. Subsequent therapies following disease progression in men with CRPC include abiraterone or Enzalutamide in men who have received ADT plus docetaxel, or Enzalutamide or docetaxel in men who have progressed on ADT plus abiraterone. Men who progress on ADT alone and become castrate-resistant are generally offered abiraterone or Enzalutamide as second line therapy. Other approved therapies for men with CRPC include docetaxel chemotherapy, Sipuleucel-T, Radium-223 and cabazitaxel chemotherapy [7-9]. Nevertheless, nearly all men with CRPC will eventually progress [2, 10]. Deaths from PC are typically the result of mCRPC, and historically the median survival for men with mCRPC has been less than two years [11]. With the exception of rare subpopulations with homologous recombination repair deficiency or mismatch repair defects that may respond preferentially to PARP inhibitors or immune checkpoint blockade, respectively, alternative targetedtherapies for prostate cancer are lacking [12-14].

MET and VEGFR2 signaling in prostate cancer
Beyond AR signaling, PC growth can be effect through targeting the MET and VEGFR2 signaling

pathways. The receptor tyrosine kinase MET plays important roles in cell motility, proliferation, and survival, and has been shown to be a key factor in tumor angiogenesis, invasiveness, and metastasis. Prominent expression of MET has been observed in primary and metastatic PCs [15, 16] with evidence for higher levels of expression in bone metastases compared to lymph node metastases or primary tumors [17, 18]. Overexpression of hepatocyte growth factor (HGF), the ligand for MET, has also been observed in PC [19], and increased plasma levels of HGF in CRPC are associated with decreased overall survival [20].

Data from preclinical studies suggest that both HGF and MET are regulated by the AR signaling pathway in prostatic tissue [15, 21, 22]. MET expression increases substantially in androgen-sensitive tumor cells after androgen withdrawal [15, 21, 22]. Administration of a MET kinase inhibitor after castration reduced tumor cell proliferation in a preclinical model of CRPC [21]. These observations indicate that upregulation of MET signaling may be associated with and contribute to the emergence of resistance to androgen suppression in PC.

Vascular endothelial growth factor (VEGF) and its receptors are key mediators in the process of tumor neoangiogenesis, invasion, and metastasis [23]. In PC, elevated VEGF in either plasma or urine is associated with shorter overall survival [24, 25]. VEGF may also play a role in activating the MET pathway in tumor cells by binding to neuropilin-1, which is frequently upregulated in PC and appears to activate MET in a co-receptor complex [18]. Agents targeting the VEGF signaling pathway have demonstrated activity in some patients with CRPC [26].

Neuroendocrine prostate cancer (NEPC)
NEPC develops *de novo* in some patients and in up to 15–20% of patients with metastatic prostate cancer treated with androgen deprivation therapy. In a review of 87 patients with NEPC retrospectively identified at Weill Cornell Medicine (WCM) between 2004 and 2017, 75% of patients with *de novo* NEPC and 92% of patients with treatment related NEPC had liver metastases at the time of diagnosis of NEPC, respectively (Eur J Cancer . 2019 Nov:121:7-18). Dependence on androgen receptor (AR) signaling is lost as tumors progress from a prostate adenocarcinoma to a NEPC histology, typically manifest by downregulation of AR, PSA, and PSMA expression in tumors (Curr Oncol Rep. 2021 Jan 12; 23(2):15). Genomic analyses from patient biopsies combined with preclinical modeling has pointed to loss of tumor suppressors RB1 and TP53 as important genomic events that contribute toe NEPC development. Treatment related NEPC is resistant to most therapies and has a poor prognosis with a median survival of less than one year from diagnosis.

2.2 Investigational Agent

Cabozantinib is a kinase inhibitor that targets receptor tyrosine kinases including MET, VEGFR -1 (Flt-1),VEGFR-2 (KDR) and VEGFR-3 (Flt-4), RET, KIT, TRKB, FLT-3, AXL, and TIE-2 with variable potencies (Table1; [27]). These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment. Cabozantinib is FDA approved for treatment in renal cell carcinoma and medullary thyroid cancer.

Table 1. *In vitro* kinase inhibition profile of cabozantinib

Kinase	$IC_{50} \pm SD$,[a] nmol/L	Enzyme concentration, nmol/L	ATP concentration, μmol/L	Assay
VEGFR2	0.035 ± 0.01	0.05	3	A
MET	1.3 ± 1.2	10	1	C
MET (Y1248H)	3.8	13	1	C
MET (D1246N)	11.8	12	1	C
MET (K1262R)	14.6	12	1	C
RET	5.2 ± 4.3	15	2	C
TIE2	14.3 ± 1.1	15	5	R
AXL	7	TBD	TBD	TBD
FLT3	11.3 ± 1.8	0.5	1	C
KIT	4.6 ± 0.5	1	3	A
RON	124 ± 1.2	60	1	C

Abbreviations: A, AlphaScreen; C, Coupled luciferase; R, radiometric; TBD, to be determined.
[a]Mean ± SD of at least 3 independent determinations.

2.2.1 Cabozantinib in prostate cancer

Preclinical activity

Inhibition of the kinase targets of cabozantinib has been shown to affect both osteoblast and osteoclastactivity, limiting the growth of bony lesions in xenograft models of mCRPC [28]. Earlier in vitro work illustrated that androgen-insensitive PC cell lines had greater c-MET ligand HGF expression versus androgen-dependent lines and, furthermore, deprivation of androgen caused upregulation of c-MET [15]. Understanding of the in vivo mechanism has further been enhanced, with demonstration that the drug's effect may be potentiated by interactions with immune and bony microenvironments, and data revealing a more dramatic effect in vivo than in vitro. For example, Patnaik et al. demonstrated that cabozantinib eliminated invasive PTEN-/p53- mouse model only when chemotaxis of neutrophils was left intact [29]. Additionally, cabozantinib increases Treg infiltration, immune recognition, and T-cell mediated killing by upregulating MHC-1 molecules and markers *(e.g.* ICAM-1, Fas) in a VEGR2- and MET-expressing cell line [30]. Furthermore, cabozantinib alone or in combination with immune checkpoint blockade decreases myeloid-derived suppressor cells (MDSCs), which are associated with a tumor permissive microenvironment, which increases immune surveillance [31, 32]. Design and interpretation of future studies must recognize that interactions with the immune and tumor microenvironment may potentiate drug effects.

Clinical studies

Based on preclinical data suggesting cabozantinib had anti-tumor activity in PC, a series of Phase I and II clinical trials were performed in unselected patients with CRPC and demonstrated that cabozantinib treatment in patients with CRPC resulted in high rates of pain relief and reductions in or discontinuations of narcotic use, along with evidence of substantial anti-tumor activity including bone scan resolution, soft-tissue lesion reduction and 12-week disease control [33]. In one phase II randomized discontinuation trial in patients with CRPC, 72% of patients exhibited regression in soft-tissue lesions, whereas 68% of patients had improvement in technectium-99m bone scan response, including complete resolution in 12%. The trial exhibited a median progression-free survival (PFS) of 23.9versus 5.9 weeks for the cabozantinib and placebo-treated cohorts, respectively, with significant reductions in bone turnover markers and bone pain with cabozantinib treatment [28].

These observations led to the phase III multicenter, randomized COMET-I trial to evaluate the effect ofcabozantinib compared to prednisone in men with previously treated metastatic CRPC. These patients had bone-dominant disease and exhibited disease progression on docetaxel-containing

chemotherapy and abiraterone or enzalutamide with the primary endpoint being overall survival (OS)[34]. No molecular markers were assessed in PC tissue or bone to determine if a molecular target of cabozantinib was amplified or mutated. A total of 1,028 patients were randomly assigned to cabozantinib (n = 682) or prednisone (n = 346). The primary endpoint of improvement in OS was not met with the median OS 11.0 months with cabozantinib and 9.8 months with prednisone (hazard ratio, 0.90; 95% CI, 0.76 to 1.06;stratified log-rank p = 0.213). Analysis of secondary endpoints however showed (1) radiographic progression free survival rPFS) was improved in the cabozantinib group (median, 5.6 v 2.8 months; hazard ratio, 0.48; 95% CI, 0.40 to 0.57; stratified log-rank p < 0.001); (2) the favorable CTC conversion rate (defined as > five CTCs at baseline to < five CTCs as best post baseline result) was 33% for cabozantinib and 6% for prednisone; and (3) Bone scan response at week 12 per an independent radiology review committee was 42% (95% CI, 38% to 46%) with cabozantinib and 3% (95% CI, 1% to 5%)with prednisone (unstratified and stratified Cochran-Mantel-Haenszel p < 0.001 for both).

Cabozantinib was not associated with improved PSA response or time to PSA progression. A PSA response, defined as a reduction of 50% or more in PSA level, occurred in 6% of cabozantinib-treated patients and 2% of prednisone-treated patients. The median time to PSA progression was 4.2 and 3 months with cabozantinib and prednisone, respectively (unstratified HR, 0.95; p = 0.639). Because COMET-1 failed to meet is primary endpoint, further development of cabozantinib in the treatment of men with CRPC was halted, and another trial, COMET-2 focused on pain palliation as the primary endpoint for cabozantinib versus mitoxantrone-prednisone in patients with symptomatic bone metastases using patient-reported outcome measures. The study was discontinued after 119 patients were randomized. In this study, cabozantinib did not demonstrate better pain palliation than mitoxantrone-prednisone in heavily pretreated patients with mCRPC and symptomatic bone metastases[35]. A recent analysis of pooled data from patients enrolled on COMET-1 and COMET-2 trials demonstrated that, after adjusting for prognostic factors, cabozantinib use was associated with better overall survival (hazard ratio 0.80, 95% confidence interval 0.67–0.95; p = 0.012)[36].

The CONTACT-02 study was a phase 3 pivotal study evaluating cabozantinib in combination with atezolizumab compared with a second novel hormonal therapy in patients with mCRPC and measurable extra-pelvic soft tissue disease who have progressed on one prior ADT. Results presented at ASCO GU in January 2024 showed that at a median follow-up of 14.3 months, the median PFS was 6.3 months for cabozantinib in combination with atezolizumab compared with 4.2 months for second line novel hormonal therapy (hazard ratio (HR) was 0.65 (95% confidence interval [CI]: 0.50-0.84; p=0.0007). At a median follow-up of 12.0 months for the ITT population, the median overall survival was 16.7 months for cabozantinib in combination with atezolizumab compared with 14.6 months for second novel hormonal therapy (HR: 0.79; 95% CI: 0.58-1.07; p=0.13). Most impressive was the cohort of patients with liver metastases where the median PFS was 6.2 months for the combination of cabozantinib and atezolizumab compared with 2.1 months in patients receiving a second novel hormonal therapy (HR 0.43 (0.27-0.68). The OS was 16.4 months versus 9.8 months (HR 0.60 (0.35-1.02) in the treatment and control arms, respectively. These data suggest that patients with liver metastases are more likely to respond to cabozantinib. The contribution of atezolizumab to the prolonged rPFS is unclear. Of note, in the CONTACT-02 study, liver biopsies were not performed so it is unknown if any patients had NEPC in their liver metastases.

2.3 Rationale

Despite the fact that dramatic improvements in bone scans and pain were observed in some patients with cabozantinib in the COMET-1 and 02 trials, it is unclear why secondary endpoints, including most notably rPFS, did not translate into improved OS. This fact may reflect that unselected patients with relatively insensitive tumors were included in the study population, given that the subjects were not

evaluated for the presence of amplifications of or activating mutations in gene targets of cabozantinib prior to enrollment. Increasing availability of genomic analyses of metastatic PC specimens and/or cell free tumor derived DNA makes possibleselection of study subjects with presumed dependence on cabozantinib targets (*i.e.*, presence ofamplifications or activating mutations). Analysis of expression profiling of metastatic PC specimens fromWeill Cornell has shown increased expression of cabozantinib's target genes MET and KIT in a significant percentage of metastatic tumors (unpublished data). VEGF alterations are found in 1-4% by DNA amplification and as much as >5% by RNA overexpression. Additionally, publically available data report the presence of mutually-exclusive qualifying mutations or activating mutations in ~17% of patients (SU2C mCRPC cohort). We predict that targeting a molecularly-defined patient cohort will identify the patient population that most benefits from cabozantinib therapy, as reflected in prolonged rPFS and OS,and more frequent PSA declines and CTC conversions.

2.4 Risk/Benefit Assessment

This is a phase II clinical trial with the primary endpoint to assess rPFS in a genomic target-selected patient population. Based on prior experience of treating unselected CRPC patients with cabozantinib, we anticipate that a significant proportion of patients that are biomarker-selected or have liver metastases will benefit from cabozantinib therapy. The expected toxicities include diarrhea, high blood pressure, hand-foot

syndrome, fatigue, nausea, decreased appetite, and painful mouth sores. It is noted with any molecular test, like those proposed to gain molecular qualification for this trial, has implicit risks of false positive results. In this case a subject may forego alternative therapies under the apprehension of possible enhanced likelihood of benefit from cabozantinib. The Informed Consent Form includes discussion of such risks.

2.5 Correlative Studies Background

Cell-free DNA

Measurement of cell-free or circulating tumor DNA (ctDNA) in plasma is a noninvasive method to molecularly analyze and characterize a patients' tumor. In addition, it allows repeated longitudinal sampling. In the current study, we aim to define the spectrum and frequency of genomic changes found in plasma DNA of patients with mCRPC prior to cabozantinib therapy and determine types and frequencies of genomic mutations that arise with treatment. In collaboration with Dr. Himisha Beltran, we will collect plasma samples and then analyze them using the PCF SELECT (Specific Evaluation in Liquid biopsies of Established prostate Cancer Targets) plasma ctDNA assay. This is a custom designed prostate cancer specific panel including 74 target genes, 42 control genes covering both exonic regions and informative single nucleotide polymorphisms (SNPs) optimized for the detection of CRPC aberrations including estimation of copy number in ctDNA. PCF SELECT (tumor DNA from cfDNA and germline control) will be run at baseline, on therapy (at 3 months), and at clinical progression.

Immune Biomarkers

Preclinical studies in a PTEN/p53-deficient murine PC model showed that cabozantinib rapidly eradicated poorly differentiated tumors [29]. This anti-tumor effect was associated with enhanced release of neutrophil chemotactic factors from tumor cells, predominantly CXCL12 - resulting in robust infiltration of neutrophils into the tumor. This study suggested that cabozantinib triggered a neutrophil-mediated anticancer innate immune response.

Cabozantinb also increased Treg infiltration, immune regulation, and T-cell mediated killing by upregulating MHC-I molecules and markers (*e.g.* ICAM-1, Fas) in a VEGFR2- and MET-expressing cell line [30]. Furthermore, cabozantinib alone or in combination with immune checkpoint blockade decreases myeloid-derived suppressor cells (MDSCs), which are associated with a tumor permissive

microenvironment, which increases immune surveillance [31, 32].

In order to test the systemic effects of cabozantinib treatment in PC patients on immune signals and cytokines related to possible immunity-dependent effects of cabozantinib, we will assess gene expression and immune cell infiltrates at baseline and after initiation of cabozantinib treatment. We will also measure circulating levels of cytokines. The primary hypothesis will be that treatment will reduce systemic levels of cytokines associated with a suppressive myeloid microenvironment. To that end, we will quantify pre and on treatment levels of the following cytokines: interleukin-8, interlukin-6 and interleukin-1 all of which have been associated with a non-permissive tumor microenvironment. As a secondary hypothesis, we will test whether levels of pro-inflammatory cytokines are increased in a compensatory manner – those studies will focus on the TH1 cytokines particularly interferon gamma, interleukin-12 and interleukin-2. Of note, prior studies by our group suggested that a TH1 cytokine signature was associated with a decreased risk of prostate cancer progression in a population-based study.

3. STUDY DESIGN

3.1 Overall Design

The hypothesis for this trial is that cabozantinib has anti-tumor activity in a molecularly-selected group of patients with CRPC or patients with liver metastases. This is a single-arm, open-label Phase II multi-institutional trial in 30 patients that have been molecularly selected based on that their tumors possess alterations in molecular targets of cabozantinib. Patients will be treated be continuously until they develop radiographic progression or discontinue cabozantinib for toxicity. If 6 or more out of 12 subjects with particular mutation or gene amplification show progression prior to 6 months, accrual for the particular genomic alteration may close. In addition, a series of correlative studies will be performed including tissue biopsies in order to further define the mechanisms of cabozantinib anti-tumor action in prostate cancer and identify surrogate markers of response.

3.2 Scientific Rationale for Study Design

Cabozantinib has demonstrated anti-tumor efficacy in a significant proportion of unselected patients with mCRPC. Testing the effect of cabozanitinb in an enriched patient population with an alteration in a molecular target of cabozantinib may increase the objective response rate. In addition, a proportion of patients with liver metastases appear to benefit from cabozantinib. Identifying biomarkers in liver metastases which correlate with response to cabozantinib would allow more rationale and targeted patient selection.

3.3 Justification for Dose

The FDA approved dose for cabozantinib for other approved indications is 60 mg, but recent data from Exelixis indicates efficacy at 40 mg daily in men with castrate resistant prostate cancer. Dose reductions for toxicity will follow established guidelines.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Assessments (SoA), Section 6.1. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. SUBJECT SELECTION

4.1 Study Population

Men with metastatic CRPC who have had disease progression following prior AR pathway-directed therapy and who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Age >18 years.
2. Documented histological or cytological diagnosis of prostate carcinoma.
3. Evidence of metastatic PC on imaging (bone scan and/or CT/MRI scan)
    a. Patients with liver metastases must have biopsy proven evidence of metastatic prostate cancer in the liver
4. Agree to undergo a biopsy of at least one metastatic site or primary prostate prior to beginning therapy. Adequate archival metastatic tissue can be used if available in lieu of a biopsy if done when patient had CRPC and within 6 months the start of treatment.
5. Agree to undergo a biopsy of at least one metastatic site or primary prostate after 3 weeksof therapy (biopsy must be between day 21 and day 24 of treatment). Re-biopsy of same pre-treatment biopsy soft tissue site especially liver metastases is preferred.
6. Serum testosterone level less than 50 ng/dl. Subjects without prior orchiectomy must be currently taking and willing to continue luteinizing hormone-releasing hormone (LHRH) analogue (agonist or antagonist) therapy until permanent discontinuation of study treatment.
7. Documented progressive metastatic CRPC based on at least one of the following criteria:
    a. PSA progression according to Prostate Cancer Working Group 3 (PCWG3) criteria
    b. Objective radiographic progression, according to PCWG3 criteria
8. ECOG performance status of 0-1
9. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments,unless specified below or AE(s) are clinically nonsignificant and/or stable on supportive therapy.
10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria **within 14 days before first dose of study treatment**:
    a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support
    b. White blood cell count ≥ 2500/mm^3 (≥ 2.5 GI/L)
    c. Platelets ≥ 100,000/mm^3 (≥ 100 GI/L) without transfusion.
    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L)
    e. Total bilirubin ≤ 1.5 × ULN (for subjects with Gilbert's disease ≤ 3 × ULN)
    f. Serum albumin ≥ 2.8 g/dl
    g. Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:
        i. If urine dipstick is positive, then:
            1. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol)
11. Patients without liver metastases must have evidence of amplification or activating mutation of selected targets of cabozantinib (including MET, KIT, RET, VEGFR-1, VEGFR-2, VEGFR-3, FLT3, AXL, TRKB, or TIE2) by **at least one** of the following (See Section 4.4 for full detail):
    a. DNA sequencing of metastatic tumor biopsy specimen or cfDNA test
    b. RNA sequencing of metastatic tumor biopsy specimen
    c. Commercial cell-free DNA assay
    d. Overexpression by IHC on metastatic tumor biopsy specimen

12. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception *(e.g.*, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after thelast dose of study treatment
13. Capable of understanding and complying with the protocol requirements and must havesigned the informed consent document.

4.3 Exclusion Criteria

1. Prior treatment with cabozantinib
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinaseinhibitor) within 2 weeks before first dose of study treatment.
3. Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) except agents to maintain castrate status within 4 weeks before first dose ofstudy treatment. Antiresportive bone agents are also allowed.
4. Subject has received abiraterone acetate or enzalutamide within 2 weeks beforeenrollment.
5. Radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
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 prior to first dose of study treatment after radiotherapy or at least 4 weeks prior to first dose of study treatment after major surgery (e.g., removal or biopsy of brain metastasis). Subjects must have complete wound healing from major surgery or minor surgery before first dose ofstudy treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment for neurological indications at the time of first dose of study treatment.
7. Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g.,clopidogrel). Allowed anticoagulants are the following:
    a. Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
    b. Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose ofstudy treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
8. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 x the laboratory ULN **within 14 days before the first dose of study treatment**.
9. The subject has uncontrolled, significant intercurrent or recent illness including, but notlimited to, the following conditions:
    a. Cardiovascular disorders:
        i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) >140 mm Hg systolic or >90 mm Hg diastolic despite optimalantihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI),or other ischemic event, or thromboembolic event (*e.g.* deep venous thrombosis, pulmonary embolism) within 6 months before first dose.
    b. Gastrointestinal (GI) disorders including those associated with a high risk of

perforation or fistula formation:

i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (*e.g.*, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastricoutlet obstruction.

ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominalabscess within 6 months before first dose.
Note: Complete healing of an intra-abdominal abscess must be confirmed beforefirst dose.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5mL) of red blood, or other history of significant bleeding (*e.g.*, pulmonary hemorrhage) within 12 weeks before first dose.

d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

e. Lesions invading or encasing any major blood vessels. Subjects with lesions invadingthe intrahepatic vasculature, including portal vein, hepatic vein, and hepatic artery, are eligible.

f. Other clinically significant disorders that would preclude safe study participation.

i. Serious non-healing wound/ulcer/bone fracture.

ii. Uncompensated/symptomatic hypothyroidism.

iii. Moderate to severe hepatic impairment (Child-Pugh B or C).

10. Major surgery (*e.g.*, GI surgery, removal or biopsy of brain metastasis) within 8 weeks beforefirst dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (*e.g.* simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment [add referencefor Fridericia formula].
Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used todetermine eligibility.
12. Inability to swallow tablets.
13. Previously identified allergy or hypersensitivity to components of the study treatmentformulations.
14. Diagnosis of another malignancy within 2 years before first dose of study treatment, exceptfor superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy.

4.4 Molecular Eligibility

To be eligible, a patient's tumor must have evidence of gene amplification, an activating mutation, or overexpression of one of the following genes: MET, KIT, RET, VEGFR-1, VEGFR-2, VEGFR-3, FLT3, AXL, TRKB, or TIE2. In the event of activating mutations, the observed mutation must be of Level 1, Level 2, or Level 3 as annotated by OncoKB (www.oncokb.org). Eligibility can be met by **at leastone** of the following diagnostic tests:

1) DNA sequencing of a metastatic tumor biopsy specimen showing gene amplification or activating mutation using a CLIA-certified assay. Tumor tissue samples must have been collected within 6 months of enrollment.
2) Protein overexpression in a metastatic tumor biopsy specimen determined by immunohistochemistry (IHC) showing 3+ protein expression using a CLIA-certified assay. These

include common in-house KIT and commercial reference labs for panTRK (*e.g.* NeoGenomics) and cMET (*e.g.* NeoGenomics, Caris, Mayo Clinic).

3) CLIA-certified commercial cell free DNA assay (either Guardant360 or FoundationOneLiquid assay) reporting gene amplification or activating mutation *within 6 months of enrollment*.
    a. For the Guardant360 Liquid Biopsy amplification must be at least (++) or (+++) for to meet eligibility.
    b. For the FoundationOneLiquid assay, amplification will be eligible. Reports that have an "equivocal" or "subclonal" designation will not be eligible.
4) Any non-CLIA certified assay such as RNA expression profiling of a metastatic tumor biopsy specimen showing overexpression must be confirmed by a CLIA-certified assay *(i.e.*, immunohistochemistry showing 3+ protein expression)

Patients who do not meet molecular eligibility criteria will be allowed to enroll if they have liver metastases that meet RECIST criteria for measurable disease. Patients with prostate adenocarcinoma or NEPC will be allowed to enroll.

4.5 Lifestyle Considerations

As food increases exposure levels of cabozantinib, subjects should fast (with the exception of water) for at least 2 h before taking their dose of cabozantinib. After the 2-hour fast, 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.

4.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of not having a molecular abnormality may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.7 Strategies for Recruitment and Retention

The study will be performed in the Prostate Cancer Clinical Trials Consortium, which consists of over 40 academic and affiliated sites across the U.S. Approximately eight PCCTC sites will participate in the trial. Patients diagnosed with documented progressive metastatic CRPC disease who are visiting Oncology Clinics of participating institutions or other for their standard of care visit will be approached for recruitment for this study. Investigators or delegates under their direct supervision may perform pre–screening of these potential subjects.

Recognizing that many centers (both in and out of the PCCTC in the NYC area) perform genomic sequencing as standard of care in men with CRPC, we will inform PCCTC members and other colleagues about this molecular selected trial to encourage referrals for this study. This will be done via email and at PCCTC meetings (at GU ASCO, ASCO Annual Meeting and PCF Annual Retreat). We will also submit a "clinical trials in progress" poster for presentation at ASCO Annual Meeting.

5 REGISTRATION PROCEDURES

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-Sites)

Subjects will be centrally registered Monday through Friday from 9:00am to 4:00pm with the Weill Cornell Medicine Joint Clinical Trials Office (JCTO). To register a new study subject, email the following documents to JCTOIIT@med.cornell.edu:

- Completed WCM subject registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Redacted source documentation to verify eligibility

Note that attachments larger than 4.5 MB are not accepted, so larger attachments should be split into more than one email. Central registration information is reviewed and entered into REDCap Cloud.

6 STUDY PROCEDURES

6.1 Schedule of Assessments

The study flow chart, including all procedures to be performed during the study, is presented below. Prior to engaging in any study procedure, each patient must sign and date an informed consent form. The following schedule of assessments applies to all subjects; assessments that are more frequent should be obtained if clinically indicated. Cycles are scheduled to be 28 days in length.

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.

	Screening	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4 +**	**End of Treatment**	**Survival Follow-Up**
Cycle = 28 days	Day -30 to -1	Day 1	Day 14	Day 21 (+ 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Post-Treatment	
Informed consent	X								
Medical History [1]	X								
Physical Exam [2]	X	X			X	X	X	X	
Vital Signs	X	X	X		X	X	X	X	
Demographics	X								
ECOG Performance Status	X	X			X	X	X	X	
ECG	X								
CBC w. differential and platelet count	X	X			X	X	X	X	
Complete Metabolic Panel[3]	X	X			X	X	X		
LDH	X	X					X[8]		
Lipase	X	X[4]					X[8]		

[1] Including cancer history, prior therapy including prior radiotherapy, surgical/pathological reports,
[2] Including height at baseline and weight at each subsequent visit

[3] Also include direct bilirubin with known Gilbert's syndrome

Cycle = 28 days	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4 +	End of Treatment	Survival Follow-Up
	Day -30 to -1	Day 1	Day 14	Day 21 (+ 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Post-Treatment	
UA and UPCR (24-hr urine, if indicated)	X						X[8]		
PT/INR and PTT	X								
Thyroid function tests (TSH/FT4 initially. If normal, then TSH thereafter)	X						X[8]	X	
Testosterone	X						X[8]	X	
Circulating Immune Activity Sample	X	X[4]					X[8]	X	
cfDNA[5]	X	X[4]					X[9]	X	
Tumor assessment (CT/MRI a/p, CT chest bone scan)	X						X[6]	X[6]	
PSA sample	X	X					X[8]	X	
Pre-treatment biopsy[10]	X								
On-treatment biopsy[11]				X					
Skeletal-related events[7]	X	X			X	X	X	X	

[4] cfDNA, circulating immune activity, lipase can be collected within 30 days prior to C1D1 or pre-dose C1D1

[5] When plasma DNA is collected, it should be collected as close to biopsy date as possible, including same day. In the event it is collected on the same day, the specimen should be acquired *prior* to the biopsy procedure.

[6] Every 12 weeks (± 5 days) until disease progression. For EOT, does not have to be repeated if done within 6 weeks of visit.

[7] Assess continuously until disease progression

[8] Every 12 weeks beginning with C4D1 (e.g. C4, C7, C10, etc).

[9] Collect only on C4D1

[10] Pre-treatment biopsy can be waived provided that adequate archival material for molecular analyses available from biopsy performed within 3 months of enrollment

[11] On-treatment biopsy during cycle 1 after 3 weeks of therapy. Biopsy must be performed between day 21 and day 24 on therapy (inclusive). *NB: cabozantinib must be held 5 days before and 5 days after biopsy*

Cycle = 28 days	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4 +	End of Treatment	Survival Follow-Up
	Day -30 to -1	Day 1	Day 14	Day 21 (+ 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Post-Treatment	
Concomitant medications[12]	X	X			X	X	X	X	
Adverse events [13]	X	X	X		X	X	X	X	
Health Care Resources [14]	X	X			X	X	X	X	
Cabozantinib dosing [15]		X			X	X	X		
Dispense/return of oral study drug and compliance accounting		X			X	X	X	X	
Additional cancer treatment, survival status								X	Subjects will be followed every 12 weeks for 2 years after completion of the study or until death, whichever occurs first

[12] Document those taken from 30 days prior to treatment through 30 days after the decision to discontinue study treatment

[13] Document new or worsening events from time of informed consent through 30 days after the last dose of study treatment (related SAEs at any time). Adverse events information will be collected at study visits and may also be collected at any time over the phone or by spontaneous subject report. At study visits where any study treatment is administered, adverse events will be documented pre- and post-dose. Certain AEs and all SAEs that are ongoing 30 days after last dose of study treatment are to be followed until resolution or determination by the investigator that the event is table or irreversible.

[14] Collection of hospital admissions, length of stay, and relevant procedures.

[15] Cabozantinib taken once daily at home

6.2 Screening Visit
(Day -30 to -1 days before start of treatment)

- Informed Consent
- Demographics
- Medical History
    - Previous therapy
    - Surgical report will include date and type of surgery +/− lymphadenectomy
    - Medication history
    - Radiotherapy report will include modality of therapy with prescribed dose and field and dates oftherapy
- Previous systemic (hormonal, chemo, other) therapy – drugs, doses, dates of therapy
- Complete Physical Exam including height and weight
- Vital Signs
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- Testosterone
- Thyroid function tests (TSH/FT4)
- PT/INR and PTT
- UA and UPCR
- EKG
- Circulating Immune Activity sample (may be collected at screening or pre-dose C1D1)
- cfDNA (may be collected at screening or pre-dose C1D1)
- CT or MRI abdomen/pelvis
- CT chest
- Bone scan
- A biopsy of at least one metastatic site or primary prostate prior to beginning therapy. However, adequate archival metastatic tissue can be used if available in lieu of a biopsy if done whenpatient had CRPC and within 3 months

6.3 Cycle 1, Day 1

- Physical Examination with vital signs and weight
- ECOG Performance Status
- CBC with differential and platelet count
- Lipase (if not obtained during screening)
- CMP (with direct bilirubin with known Gilbert's syndrome)
- PSA
- LDH
- Concomitant medications
- Circulating Immune Activity sample (may be collected at screening or pre-dose C1D1)
- cfDNA (may be collected at screening or pre-dose C1D1)
- Skeletal-related events
- Adverse events
- Dispense oral study drug and compliance accounting

6.4 Cycle 1, Day 14

- Vital Signs
- Adverse Events

6.5 Cycle 1, Day 21: On-treatment Biopsy

Fresh tumor sample collection will occur during cycle 1 at 3 weeks of cabozantinib therapy (between days 21 and 24 of treatment, inclusive).

NOTE: **Cabozantinib must be held 5 days before and 5 days after biopsy**

6.6 Cycle 2, Day 1 + Cycle 3, Day 1

- Physical Examination with vital signs and weight
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- Concomitant medications
- Skeletal-related events
- Adverse events
- Dispense/return oral study drug and compliance accounting

6.7 Cycle 4, Day 1 +
Every 4 weeks (± 3 day(s))

- Physical Examination with vital signs and weight
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- SOC and Research scans/labs to be collected as per schedule of assessments
- Skeletal-related events
- Adverse event evaluation
- Concomitant medications
- Dispense/return oral study drug and compliance accounting

6.8 Treatment Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for cabozantinib are described in Section 7.

6.9 End of Treatment

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

- Physical Examination with vital signs and weight
- ECOG Performance Status
- CBC with differential and platelet count
- CMP (with direct bilirubin with known Gilbert's syndrome)
- Thyroid function tests
- PSA
- Testosterone
- LDH

- Concomitant medications
- Circulating Immune Activity sample
- cfDNA
- Skeletal-related events
- Adverse events
- Return oral study drug
- CT/MRI abdomen/pelvis (if not done within 6 weeks)
- CT chest (if not done within 6 weeks)
- Bone scan (if not done within 6 weeks)

6.10 Follow-up Phase

Patients will be followed every 12 weeks for two years after completion of the study or until death, whichever occurs first. Patients that have been removed from the study for serious or adverse events will be followed until resolution or stabilization of the event.

6.11 Study Intervention/Follow-up Compliance

Patients will be monitored closely by the research staff for protocol compliance, including follow up visits and imaging. Pills in the pill bottle will be returned by the patients and pills counted to assure compliance.

6.12 Lost to Follow Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

7 STUDY INTERVENTION

7.1 Study Intervention/Device Description

During the treatment phase, subjects will receive cabozantinib until either disease progression, the occurrence of drug-related toxicity, or for other reason(s) for subject withdrawal described in Section 7.9. Subjects will be instructed to immediately inform the principal investigator (PI) of any AEs.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks aredescribed in Section 7. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery. Ifrequired, appropriate dose modifications for cabozantinib are described in Section 7.7.1.

7.2 Potential Drug Interactions

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate). Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronicuse of strong CYP3A4 inducers after treatment 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

Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who hasbeen concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Reduce the dosage of cabozantinib if concomitant use with strong CYP3A4 inhibitors cannot be avoidedas detailed in the package insert.

7.3 Availability

Cabozantinib is an investigational agent that will be supplied by Exelixis.

7.4 Acquisition and Accountability

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents/device receivedfrom *Sponsor* on a Drug Accountability Record Form (DARF) or Device Log.

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, 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 study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

7.5 Formulation, Appearance, Packaging, and Labeling

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 7.1.

Table 7.1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68

Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

[a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose

7.6 Product Storage and Stability

Refer to the Investigator's Brochure for details on storage and handling of cabozantinib.

7.7 Preparation

Cabozantinib is supplied as a capsule formulation with dose strengths of 20 mg. The capsules are two-piece hard gelatin capsules with "XL184 20 mg" printed on the body of the capsule shell. No preparation is necessary.

7.8 Dosing and Administration

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The misseddose 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 notbe crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

7.8.1 Dosing Delays/Dose Modifications

The following should be taken into consideration in decisions regarding dose modifications (reductionsor 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.
- The assigned starting dose for cabozantinib is 40 mg/day. Two dose reduction levels of cabozantinib is permitted (see Table 7.2).
- Dose modification criteria for cabozantinib are shown in Table 7.2. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be

modified at any time while a subject is on treatment.

- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.
- Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

General management of cabozantinib dosing related to AEs is in Section 7.8.1 and additional guidelines for the management of specific AEs are provided in Section 7.9

Table 7.2: Dose Reductions of cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	20-mg cabozanitinib oral every other day
20-mg cabozantinib oral qd	20-mg cabozanitinib oral every other day	No dose reduction permitted

NOTE: cabozantinib will be discontinued if a every other day (eod) dose of 20 mg cabozantinib(minimum dose) is not tolerated.

Table 7.3: Dose Modifications of Cabozantinib for Treatment-Related AEs

Event	Management
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 approved by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care .
Note: The dose delay and modification criteria for specific medical conditions are provided in Section 7.7.1	

7.8.2 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 7.2 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 40 mg/day) may be allowed at the discretion ofthe investigator 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 adrug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g. central nervous system, cardiac, hepatic, renal).

7.9 General Concomitant Medication and Supportive Care Guidelines

If the subject must use other concomitant medications (including all pain medications; vitamins; herbal and nutritional supplements; and over-the-counter medications) during the period from 28 days beforetreatment through to 30 days after the decision to permanently discontinue study treatment, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in thesource documents.

Drugs used to control bone loss (e.g. bisphosphonates, denosumab) are allowed if started prior to screening activities but may not be initiated or exchanged during the course of the study. Transfusions, hormone replacement, and short-term systemic steroid treatment should be utilized as indicated by standard clinical practice while the subject is enrolled in the study.

Antacids, H2 blockers, or proton-pump inhibitors (PPIs) should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

7.9.1 Guidelines for Management of Potential Adverse Events

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. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/orinterruption for cabozantinib.

7.9.2 Cabozantinib

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting,
constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of thesafety profile of cabozantinib, refer to the cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g. transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs *(e.g.* deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess,GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome(RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia,lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose.Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.

Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductionsand treatment interruptions should be considered. Dose reductions are recommended for events that, ifpersistent, could become serious or intolerable (See Table 7.2).

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

7.9.3 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatmentwith 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 (Turnage and Badgwell 2016) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

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. Guidelines for the evaluation andmanagement of diarrhea are shown in Table 7.4. 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 agentsdoes not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dosereduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic 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.

Table 7.4: 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 (e.g. loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day])
	• Dietary modifications (e.g. small lactose-free meals, bananas and rice)
	• Intake of isotonic fluids (1-1.5 L/day)
	• Re-assess after 24 hours:
	  ○ Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval
	  ○ 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 (e.g. stool sample for culture)
	  ○ Administer antibiotics as needed (e.g. 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
	  ○ Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose
	  ○ Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g. 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

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 8.3 for further details).

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

7.9.4 Non-Gastrointestinal Fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosedwith a non-GI fistula.

7.9.5 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brainmetastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be held for 5 days before and an additional 5 days after procedures, including biopsies.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

7.9.6 Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resumingtreatment per discretion of the investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin),direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued. See Section 7.2 for additional restrictions on anticoagulation therapy.

Arterial thrombotic events (e.g. TIA, MI) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebralinfarction, or any other clinically significant arterial thromboembolic complication.

7.9.7 Hypertension

Table 7.5: Management of Hypertension Associated with Cabozantinib

Event	Management
Subjects NOT receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic)[a] and < 160 mm Hg OR > 90 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 cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <140 mm Hg systolic or <90 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment

≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose levelb or interrupt cabozantinib 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 < 140 mm Hg systolic or < 90 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. • Cabozantinib 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 cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive emergency	• Discontinue cabozantinib treatment.
[a] Permitted dose levels are defined by individual protocols. [b] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).	

The table above provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure shouldbe monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

7.9.8 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potentialrisk for complications before study treatment is initiated. Appropriate correction of local factors shouldbe instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.
During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (e.g. with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss,and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture iforal infection is suspected and treat infection as clinically indicated.

7.9.9 Skin and Subcutaneous Tissue Disorders

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications andwound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and

other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decisionto resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

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

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in the table below.

Table 7.6: Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

Event	Management
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib 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 PPE worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPE worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume cabozantinib at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from cabozantinib if PPES does not improve within 6 weeks.
[b] Permitted dose levels are defined by individual protocols.	

7.9.10 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors includeuse of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.
Osteonecrosis of the jaw (ONJ) 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 osteonecrosis. 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 interrupted 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 hassufficiently healed and the Sponsor has approved the re-initiation of therapy.

7.9.11 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR.

The table below provides treatment guidelines for proteinuria deemed related to cabozantinib. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceridelevels, and edema).

Table 7.7: Management of Proteinuria Associated with Cabozantinib

Event	Management
UPCR ≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring.
UPCR > 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days. • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting 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 interruption. • 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.

UPCR ≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h 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 cabozantinib treatment.

7.9.12 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms shouldbe assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache,visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

7.9.13 Hepatocellular Toxicity

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (e.g. liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

Cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 × ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.* International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib should be interrupted until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) canindicate drug-induced liver injury (DILI). Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.

Table 7.8: Management of Hepatocellular Toxicity Associated with Cabozantinib

Event – Elevation of ALT, AST, or Total Bilirubin (CTCAE v4)	Management
Grade 1 ALT or AST > ULN – 3.0 x ULN Bilirubin > ULN – 1.5 x ULN	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2[a,b] ALT or AST > 3.0 – 5.0 x ULN Bilirubin > 1.5 – 3.0 x ULN	• Interrupt cabozantinib if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart cabozantinib after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade 3[a,b] ALT or AST > 5.0 – 20.0 x ULN Bilirubin > 3.0 – 10.0 x ULN	• Interrupt cabozantinib and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart cabozantinib at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment.
Grade 4[b] ALT or AST > 20.0 x ULN Bilirubin > 10 x ULN	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 approved by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.
[a]Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there is less than a doubling in the aminotransferases from baseline and if there are no progressive elevations in serum bilirubin concentration or coagulation factors.	

7.9.14 Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (*e.g*. after myelosuppressive anticancer therapies, splenectomy), destructive growth ofthe underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy.Cabozantinib should be interrupted until adequate healing has taken place.

7.9.15 Blood and Lymphatic System 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. Subjects with hematologic toxicities may require additional or more frequentlaboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be appliedas clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating

growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessedimmediately and treated appropriately and in a timely manner according to institutional guidelines.

7.9.16 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after diseasespecific morbidities have been excluded when not prohibited.

7.9.17 Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibitedby a particular protocol.

7.9.18 Corrected QT 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. Review of the larger safety database(~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmedthe absence of safety concerns associated with QT prolongation. There were no events of torsades depointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increasecabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms, 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, the following actions must be taken:

- Interrupt cabozantinib treatment
- Hospitalize symptomatic subjects (e.g. with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation,and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.
  Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib 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 is not confirmed

- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinibadministration and is treatable/has been resolved
  Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2weeks for 1 month, then according to the protocol-defined time points.

Cabozantinib 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

7.9.19 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 7.3 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

7.9.20 Endocrine Disorders

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroidfunction test alterations and its clinical relevance. Management of thyroid dysfunction (e.g. symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

7.9.21 Angioedema

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

7.10 Duration of Therapy and Criteria for Removal from Study

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'swithdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Section;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception(*e.g.,* male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;

- 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 thesubject 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 allsubjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will havestudy treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined bythe investigator

At any time, the study sponsor (Exelixis) or the sponsoring institution (Weill Cornell Medicine) can terminate this study. Should this occur, 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. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practicable.

8 CONCOMITANT MEDICATIONS AND THERAPIES

8.1 Allowed Therapy

- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban,or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
    - At the time of first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed ifclinically indicated and the benefit outweighs the risk per the Investigator's discretion.
        - Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban,or apixaban are allowed if the subject has no evidence of brain metastasis, has been ona stable dose of the anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 7.2 for prohibited anticoagulants.
    - After first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed ifclinically indicated and the benefit outweighs the risk per the Investigator's discretion.
        - Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (e.g., for the treatment of DVT),and the benefit outweighs the risk per the Investigator's discretion. See section 6.3.1.3.4for management of thromboembolic complications while on study. See section 7.2 for prohibited anticoagulants.
    - Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to,

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

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g. ASCO or ESMO guidelines).
- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk perthe investigator's discretion.
    - Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates. Oral examinationsare recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- For restrictions on oral anticoagulants see Section 7.
- Potential drug interactions with cabozantinib are summarized in Section 8.3.

8.2 Prohibited or Restricted Therapy

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Any nonprotocol systemic anticancer treatment (e.g. chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).
    - The following therapies should be avoided until study treatment has been permanentlydiscontinued or until otherwise specified:
- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (e.g. epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's

Wort) may significantly decrease cabozantinib concentrations and should be avoided. 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, as this could significantly increase the exposure to cabozantinib.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, 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 8.3.

8.3 Potential Drug Interactions

Cytochrome P450: 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 concentration-vs-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 to CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib isunlikely 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 strongCYP3A4 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 (e.g. 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 (e.g. boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit 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.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:
Http://medicine.iupui.edu/clinpharm/ddis/table.aspx
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. A case of a drug-drug interaction between cabozantinib and warfarin that may involve displacement of plasma protein bound drug has been reported in the literature [41]. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions:
Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potentialto increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.
Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

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

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

9 CORRELATIVE/SPECIAL STUDIES

i. *Cell–free plasma DNA and archival tissue:*

Plasma samples for ctDNA will be collected for analysis prior to treatment (as close to biopsy timing as possible), at 12 weeks, and at progression using the PC specific platform developed in collaboration with Dr. Himisha Beltran. We will also request archival paraffin embedded tissue to incorporate tissue-based and cell free DNA approaches to assess PC pathway changes and genomic /epigenomic alterations and will correlate with clinical response. We will evaluate the association of molecular biomarkers with treatment response.

We will also compare tumor tissue targeted genomic sequencing results (CLIA test used for inclusion) with ctDNA findings at baseline and determine their concordance, identify and track these alterations, monitor ctDNA tumor content and quantify relevant tumor clones on therapy, and analyze somatic

alterations that emerge at the time of progression/therapy resistance. We predict that a molecularly defined subset of CRPC will preferentially respond to Cabozatinib and this group is detectable using plasma-based assays. These data will help develop a non-invasive blood-based method for future trial inclusion criteria, as well as provide new insights into mechanisms of response/resistance to Cabozantib in prostate cancer.

ii. *Immune Assays:*
Mandatory collection of 5 mL of plasma or serum in Serum Separation Tubes will be obtained at baseline, every 12 weeks, and at the time of disease progression. These will be aliquoted in 100 microliter fractions and stored at -80 degrees C prior to thaw for analysis.

iii. *Tumor Tissue:*
Metastatic tumor tissue biopsies will be taken with core needle or excisional biopsy. Fine needle aspiration is **not** allowed. It is encouraged that 6 core samples be collected from a single site with a minimum of 4 core samples collected. The biopsy sample will be split into two components, one formalin fixed for histological and immunohistochemical analyses, as well as possible DNA mutation analysis. The other component will be flash frozen for RNA isolation and sequencing. In addition to the typical hematoxylin and eosin staining for tumor morphology and histologic classification.

9.1 Laboratory Correlative Studies Sample Processing

Instructions for handling, preserving, and shipping the specimens are described in the Lab Manual.

10 MEASUREMENT OF EFFECT

All baseline evaluations will be performed as closely as possible to the beginning of treatment. For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

10.1 Response Criteria

In order to evaluate efficacy, all study-required tumor assessments and PSA measurements must be obtained. Baseline and all post baseline PSA assessments will be used to measure PSA response rate and time to PSA progression based on protocol-specific/modified PCWG3 criteria. Any unscheduled PSA measurement will be included in the periodic assessment of PSA progression.

Radiographic scans (CT, MRI, or bone) will be used to assess best overall response and radiographic progression based on PCWG–modified RECIST criteria for soft-tissue lesions and protocol-specific criteriafor bone lesions Baseline images should be taken during Screening as close as possible to, and never more than 28 days before, Day 1 Week 1. Every effort must be made to ensure the same radiographic method is used before and after treatment at scheduled visits.

Other disease-related signs or symptoms suggestive of progression, including escalating pain not referable to another cause, increased LFT in subjects with baseline liver metastases, increased ascites, declining performance status, and examination findings consistent with disease progression, are valid reasons to consider an unscheduled assessment of tumor status.

10.2 Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the following PCWG-modified RECIST response criteria for target(soft-tissue) lesions definitions apply.

- Complete response (CR): the disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
- Partial response (PR): a decrease from baseline ≥ 30% in the sum of the LD of all target lesions Progressive disease (PD): an increase ≥ 20% in the sum of the LD of all target lesions based on thesmallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
- Stable disease (SD) : neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum LD recorded since treatment started

10.3 PSA

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

For each patient, a waterfall plot will be used to report the percent change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment

10.4 Bone

Record post-treatment changes as either “no new lesions” or “new lesions”. In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

10.5 Duration of Response

Duration of overall response:
Duration of overall response is measured from the time when partial response or complete response isfirst noted until the date when recurrent or progressive disease is objectively documented. Duration ofoverall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

10.6 Progression-Free Survival

Radiographic progression will be assessed as per PCWG3 criteria. Radiographic progression-free survival(rPFS) is a composite endpoint defined as the time from treatment start to disease progression in bone or soft-tissue, or death, whichever occurs first. All assessments of disease should be collected at the same time interval (e.g., bone scan, CT scan, and PSA). In addition to PSA, confirm post-treatment changes in measurable target lesions, radionuclide bone scans, and symptoms.

11. DATA REPORTING / REGULATORY CONSIDERATIONS

11.1 Data Collection

The data collection plan for this study is to utilize REDCap Cloud to capture all treatment, toxicity,

efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap Cloud

REDCap Cloud is a secure web-based commercial grade electronic data capture (EDC) and management system that is 21 CFR Part 11 compliant and HIPAA compliant. It is also HITRUST and ISO27001 certified. The REDCap Cloud platform extends the features of academic REDCap to create a regulatory-compliant application with features suitable for building and managing projects ranging from online surveys and databases through Phase III clinical trials.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval ofthe appropriate regulatory bodies obtained before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before thestudy center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safetyof the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.
All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

All protocol amendments and consent form modifications will be made by the Principal Investigator. Exelixis will have the opportunity to review and approve the changes prior to submission of these changesto the local IRB and distribution to participating sites.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill CornellMedicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principlesbased on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and

local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefitsof the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws andregulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for furtherinformation on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the studyand quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents

should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, ormedical practice.

12. STATISTICAL CONSIDERATIONS

The proposed design is a single-arm, open-label, non-randomized study. The primary endpoint is radiographic progression-free survival (rPFS) defined as the time from initiation of treatment to minimum of radiographic progression or death, whichever occurs first. The historical control of median rPFS of 5.6 months (from COMET-1) would approximately translate to a 50% rPFS rate at 6 months.

The entire cohort as well as subgroup analysis by specific genomic alterations will be performed.

12.1 Study Design/Endpoints

The proposed design is a single-arm, open-label, non-randomized study. The primary endpoint is radiographic progression-free survival (rPFS) defined as the time from initiation of treatment to minimum of radiographic progression or death, whichever occurs first. We will enroll up to 28 patients with liver metastasis aimed to estimate the rPFS survival probabilities. Using the Kaplan-Meier estimator, with this sample size, we estimate the 95% CI of the median survival probability is 31.1-68.9%

Secondary endpoints include PSA decline, tumor response, and OS.

12.2 Sample Size/Accrual Rate

Sample size for the entire trial will be 30 patients. Accrual will not mandate an equal number of each of the qualifying molecular abnormalities. The sponsor retains the right to terminate enrollment in any specific genetic alteration if no significant benefit is observed in that given cohort.

Any enrolled subject who withdraws for any reason prior to a full 28 days of treatment and assuming he did undergo the second biopsy ("on treatment biopsy") will be replaced and not incorporated into the analysis.

Accrual is anticipated to be 1-4 patients per month in total across all study sites

12.3 Analysis of Endpoints

12.3.1 Analysis of Primary Endpoints

Median rPFS will be estimatedusing Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% Cls for the Kaplan-Meier estimates.

12.3.2 Analysis of Secondary Endpoints

The median OS will be estimated using Kaplan-Meier methodology. Greenwood's formula will be used to calculate 95% CIs for the Kaplan-Meier estimates. The proportion of men with a meaningful decreasein PSA from baseline (30% and 50% declines will both be used) will be summarized with a binomial pointestimate and corresponding 95% binomial CI. Likewise, the proportion of patients with a tumor response(modified RECIST response of CR or PR) will also be estimated with a binomial point estimate and 95% CI.

12.4 Analysis of Exploratory Endpoints

Data generated will include IHC scores for targets of cabozantinib, scores for immune cell infiltrate, whole exome sequencing (WES), targeted DNA sequencing, and RNA-Seq for expression. Measures withsignificant changes from baseline will be determined using the appropriate two-sample test: either a paired t-test or Wilcoxon signed rank test for continuous measures and a chi-square test for categorical variables. The Benjamini-Hochberg procedure will be used to control the false discovery rate for the genomic measurements (DNA, RNA Seq). If the variables are ordinal, an analysis will be done for the proportion of changes that were "positive", "negative", or "no change". An assessment of differences between groups (*e.g.* patients with and without tumor response) will be evaluated with a two-sample t-test or Wilcoxon rank sum test, whichever is most appropriate, for continuous measurement. A chi- square or Fisher's exact test will be used to compare categorical variables between groups of interest. A comparison of time-to-event variable between subgroups of interest will be done with a log-rank test. Associations of variables with time-to-event outcomes will be made with Cox proportional hazard models. For baseline variables the survival clock will start at baseline; for

variables measured later, a landmark analysis will be done starting the survival clock at the time the data were obtained (and removing patients who had the event of interest before that time). We will also perform a Cox regression that treats multiple measurements of a variable as time-dependent

12.5 Reporting and Exclusions

12.5.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with cabozantinib provided they have had at least 4 weeks of drug.

12.5.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least 3 cycles of therapy.

13. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with 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.

13.1.2 Adverse Events (AEs)

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 eventcan 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 after informed consent 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.

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 current version ofthe National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE).

13.1.3 Serious Adverse Events (SAEs)

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 ofdeath; it does not include an event that, had it occurred in a more severe form, might havecaused 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 staysof fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in adiagnosis 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 ofproduct dependency or product abuse.

13.1.4 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 treatmentand 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 thestudy 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 argumentsto suggest a causal relationship between the AE and study

treatment. Possibly and probably related AEs should be documented as related.

13.1.5 Serious Adverse Event Reporting

Instructions for Weill Cornell Medicine:
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 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 informed consent, even if the SAE occurs more than 30 days after the decision to discontinue studytreatment.

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 faxed to 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.

Instructions for Participating Sites:
Within 24 hours of the Investigator's knowledge of the event, participating sites must report SAE to:

- WCM by sending the following forms via email to jctoiit@med.cornell.edu attaching the following completed documents:
  - WCM SAE Cover Sheet
  - Form FDA 3500A for Mandatory Reporting (MedWatch) https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
- The SAE should be reported to the participating site's institutional regulatory board (IRB), as per institutional guidelines. Proof of submission and IRB acknowledgment should be sent via email to jctoiit@med.cornell.edu when received.
- The SAE should also be reported to Exelixis within one (1) business day of the site PI's knowledge of the event. The reports must be sent to drugsafety@exelixis.com or faxed to 650-837-7392.
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13.1.6 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-1form;

- 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 alladverse events occurring during the conduct of the study.
- The PI is responsible for complying with all regulatory authority reporting requirements for thestudy 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 caseof multi-center studies, it is the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

13.2 Other Safety Considerations

13.2.1 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 (e.g., dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

13.2.2 Medication Errors/Overdose

Any overdose, or study drug administration error that results in an AE, even if it does not meet thedefinition of serious, requires reporting within one (1) business day to Exelixis.

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

13.2.4 Investigational Agent or Device Risks (Expected Adverse Events)

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending orderof frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g. transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs *(e.g.* deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess,GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome(RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated

with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia,lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose.Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.
Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductionsand treatment interruptions should be considered. Dose reductions are recommended for events that, ifpersistent, could become serious or intolerable (Section 0).

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation,severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

13.2.5 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.2.6 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/sites/default/files/policy_forms/immediate_reporting_policy_01_2021_0.pdf

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized, and no more follow−up is required. This requirement indicatesthat follow−up may be required for some events after the patient discontinues participation from the study.

14. DATA AND SAFETY MONITORING PLAN (DSMP)

This study will utilize the Weill Cornell Medicine (WCM) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring this study for safety concerns, with ongoing updates from the Study Chair on a continuous basis.

The Weill Cornell's DSMB is comprised of medical specialists and advisors on human rights issues in human subject research. Once a protocol has been submitted and approved by the Institutional Review Board (IRB) and is recommended for oversight by the DSMB, the Board determines if the protocol will be reviewed quarterly, semi−annually, or annually.

The DSMB evaluates the accumulated data from the study in order to monitor the safety of subjects throughout the trial and reviews the risks and benefits, as well as the efficacy, of the study. The DSMB will

also evaluate the overall trial conduct and progress. Ultimately, the DSMB validates the continuationof the trial or determines if a study needs modification or termination.

Reports to the DSMB will include the following items for review:

- Completed DSMB Periodic Review Form.
- Synopsis of the study to date.
- IRB approved consent form.
- IRB current protocol.
- Summary table of study results.
- Adverse event table.
- Data safety monitoring plan.

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subject research projects and to protect the safety of human subjects. Safety monitoring can be viewed as any process during a clinical trial that involves the review of accumulated outcome data for groups of patient−subjects to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998, 2000) specify that all clinical trials should have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities will be commensurate with the nature, size, and complexity of the trial in accordance with institutional policies and will be determined after IRB and DSMB review of the protocol immediately prior to study activation. For a small, single−center study, usually a statistician in conjunction with a Safety Officer performs the monitoring. For that single−site, high−risk trials, a DSMB may be appropriate. For larger, single or multi−site studies, a committee, often called a Data Safety Monitoring Board (DSMB), usually performs the monitoring. Ongoing review of the data by an independent individual or committee assures the investigators, the IRB, the study's sponsor, and the funding agency that the trial can continue without jeopardizing subjects' safety.

Weill Cornell Medicine requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

For this study, the DSMB will be notified by immediate reports for SAEs fitting immediate reporting criteria and be reviewed in real-time. In addition, Periodic Reviews will be conducted every 6 months following enrollment of the first patient and at convened DSMC meetings.

14.1 Medical Monitor

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the appropriate committees/agencies. This individual will be a qualified physician, other than the principal Investigator, not associated with this particular study, able to provide medical care to research subjects for conditions that may arise during the conduct of this study and will monitor the subjects during the conduct of the study.

Ashish Saxena, MD PhD will serve as the Medical Monitor for this study.

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, any other records required under the Protocol, 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 (a) 2 years following the marketing application approval date for the study treatment in the indication being investigated, or (b) 2 years after the investigation is completed or discontinued, or (c) for a period of time consistent with local regulatory requirements, whichever is longest. 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.

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 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 must 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.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects should be identified by identification codes and not by their names. The investigator should keep a subject enrollment log

showing codes, names, and addresses. The investigator should maintain documents *(e.g.* subjects' written consent forms) in strict confidence.

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

17. PUBLICATION OF DATA

The Principal Investigator 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 *(e.g.*, Weill Cornell Medicine) and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

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