Status Page

PROTOCOL 11-208

Closed to New Accrual

Closure Effective Date: 01/03/2017
No new subjects may be enrolled in the study as described above.
Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted: ***01/28/16***
Date Posted: ***[01/29/2016]***

Alert Page

DF/HCC Protocol #: **11-208**

Safety / Drug (includes preparation, administration, dose modifications, equations)

Exelixis, as the study drug supplier, is in a transition phase of capsule formulation and currently both freebase tablets and salt weight capsules will be used to dose patients.

Some examples of dosing using the salt weight capsules include:

- The starting dose of 60 mg freebase of cabozantinib is equivalent to three 25 mg salt weight capsules.
- The first dose reduction of 40 mg freebase dose of cabozantinib is equivalent to two 25 mg salt weight capsules.
- The second dose reduction of 20 mg freebase dose of cabozantinib is equivalent to one 25 mg salt weight capsule.

New risk cardiac risk information has been added to the consent form. Please refer to section 6.3.10 for Guidelines for Management of Treatment Emergent Corrected QTc prolongation.

Section 8.2.2 Bone Turnover Markers

Due to the closure of the MGH Clinical Laboratory Research Core (CLRc), which previously processed bone turnover marker specimens, bone turnover markers will no longer be collected for all active and new patients.

Section 9.1 Schedule of Assessments for main study participants (cohort 1)

Footnote G: Serum/urine for bone turnover markers will no longer be collected for all active and new patients.

DFCI Protocol No: 11-208

Front Sheet

Report Generated: 08/31/2017 02:11 PM

Title: A phase II trial of cabozantinib in women with metastatic hormone-receptor-positive breast cancer with involvement of bone

Overall Institution: Massachusetts General Hospital

Overall Principal Investigator	Email	Institution
Isakoff, Steven J	SISAKOFF@PARTNERS.ORG	Massachusetts General Hospital

Site Responsible PI(s)	Email	Institution
Come, Steven E.	scome@caregroup.harvard.edu	Beth Israel Deaconess Medical Center
Tolaney, Sara M	STOLANEY@PARTNERS.ORG	Dana-Farber Cancer Institute

Primary Contact(s) for Questions	Email	Phone
Sutherland, Sara	ssutherland1@partners.org	617-643-5415

Sponsor Name	Sponsor Protocol No	Roles	Grant Number(s)
Exelixis	XL184-IST12	Funding	
DF/HCC Investigator		Regulatory	
Dana-Farber/Harvard Cancer Center		Funding	

Total Study-Wide Enrollment Goal: 75 **Total DF/HCC Estimated Enrollment Goal:** 70

Phase: II

Age: Adults

Age Ranges: Age-Adults (18-64); Age-Adults (65+)

Will all subjects be recruited from pediatric clinics?

CTEP Study: No

Management Group(s): BIDMC Breast Cancer
DF/HCC Breast Cancer
DF/HCC Satellite Site
DFCI/BWH Breast Oncology
MGH Breast Cancer
MGH Regulatory Coordinators
OTHER Registering Site

Primary Management Group: DF/HCC Breast Cancer

Investigational Drug? Yes

Drug(s), Biologic(s): FASLODEX, XL184

IND #: 112433

IND Holder Type: DF/HCC Investigator

IND Holder Name: Michaela Higgins

Investigational Device? This study does not use an Investigational Device.

IRB of Record:

Risk Category: Greater Than Minimal Risk

Protocol Involves: Human Material Collection; Medical Record Review; Questionnaires/Surveys/Interviews; Radiological Exams
Other Reason: RTK Inhibitor

Date Range: (Medical Record Review and Specimen Collection studies)

Participating Sites under the DFCI IRB

Institution: Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Dana-Farber Cancer Institute
Dana-Farber Cancer Institute at Faulkner
Massachusetts General Hospital

Participating Institutions Under Other IRB

Institution: Memorial Sloan-Kettering Cancer Center **Location:** NEW YORK, NY

Protocol Number: 11-208

Approval Date: 09/06/11 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 10/25/11 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OHRS Version Date
10/31/11	Alert Page added due to Amendment #3 at MGH only	10/27/11	-
12/15/11	Delayed Activation Alert Page removed: DFCI and BIDMC now ready for activation (Note: previously activated at MGH on 10/25/2011; all sites ok)	N/A	-
01/23/12	Front Sheet replaced due to Amendment #4	01/12/12	-
01/27/12	Consent Form and Front Sheet replaced due to Amendment #6 (Note: re-consenting required)	01/17/12	-
02/16/12	Protocol, Alert Page and Front Sheet replaced due to Amendment #5	01/23/12	-
03/05/12	Consent Form and Front Sheet replaced due to Amendment #7	02/17/12	-
03/26/12	Consent Form replaced due to Amendment #10	03/22/12	-
03/26/12	Protocol and Front Sheet replaced due to Amendment #8	03/09/12	-
05/03/12	Protocol, Consent Form, Alert Page and Front Sheet replaced due to Amendment #11	04/27/12	-
05/09/12	Front Sheet replaced due to Amendment #9	04/30/12	-
06/05/12	Correction: Consent Form and Front Sheet replaced to reflect current study staff	N/A	05/22/12
06/20/12	Protocol, Consent Form and Front Sheet replaced due to Amendment #12 & 13	06/19/12	06/19/12
07/23/12	Consent Form replaced due to Amendment #14	07/16/12	07/19/12
07/26/12	Front Sheet replaced due to Amendment #15	07/26/12	n/a
08/13/12	Study renewal/Consent Form footer replaced due to Continuing Review #1	08/09/12	N/A
09/14/12	Front Sheet replaced due to Amendment #17	09/12/12	N/A
10/11/12	Protocol, Consent Form (CR 1 most recent approval date) and Front Sheet replaced due to Amendment #16	08/06/12	10/11/12
11/16/12	Consent Form replaced due to Amendment #18	11/15/12	11/16/12
11/29/12	Temporary closure at DFCI site: due to Administrative hold (Note: BIDMC,FAU,MGH,SKC sites remain open)(effective 11/26/12; Amendment #19)	11/29/12	N/A
12/07/12	Study closed – Study accrual goal met	12/07/12	N/A
12/28/12	Front Sheet replaced due to Amendment #20	12/11/12	N/A
01/08/13	Correction AM #20: Re-open to accrual due to increase in accrual goal	N/A	N/A
03/01/13	Administrative Update #1: Pharmacy Manual added	N/A	N/A
03/22/13	Consent Form replaced due to Amendment #23	03/22/13	03/22/13
04/08/13	Consent Form replaced due to Amendment #24	04/04/13	04/08/13
04/23/13	Consent Form replaced due to Amendment #25 (note: re-consent is required)	04/15/13	04/23/13
05/30/13	Protocol, Consent Form and Front Sheet replaced due to Amendment #26	05/16/13	05/30/13
06/19/13	Administrative Update #2/ Front Sheet replaced due to IDB	N/A	N/A
08/01/13	Administrative Update #3: Front Sheet replaced due to updated IB	N/A	N/A
08/01/13	Amendment #22 (no changes to online documents)	04/02/13	n/a

08/01/13	Front Sheet replaced due to Amendment #27	08/01/13	n/a
08/08/13	Study renewal/ Consent Form replaced due to Continuing Review #2	08/08/13	08/08/13
08/20/13	Correction: Front Sheet replaced due to overlap of administrative update submission	N/A	N/A
08/30/13	Protocol, Cabozantinib/Fulvestrant Cohort Consent Form and Front Sheet replaced; Main Consent Form and 28 Day Drug Diary added due to Amendment #28 (note: re-consent is required)	08/20/13	08/22/13
09/12/13	Local Appendix added due to Amendment #29	09/05/13	N/A
09/30/13	Front Sheet replaced due to Amendment #30	09/30/13	N/A
11/15/13	Protocol, Consent Forms and Front Sheet replaced; Pain Questionnaire added due to Amendment #31 (note: re-consent is required)	11/08/13	11/15/13
11/21/13	Protocol and Front Sheet replace due to Amendment #32	11/11/13	N/A
11/22/13	Correction AM #31: Protocol and Front Sheet from AM #31 reposted	N/A	N/A
12/31/13	Permanent Closure to New Accrual due to safety issues or concerns (effective date: 12/16/13; Amendment #33)	12/31/13	N/A
07/22/14	Cabozantinib / Fulvestrant Consent Form, Protocol and Front Sheet replaced due to Amendment #36	07/22/14	07/22/14
07/31/14	Reopen to new accrual due to Amendment #34	05/15/14	n/a
08/08/14	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired 08/08/14.	N/A	N/A
11/05/14	Remove Hold. Study renewal/ Consent Form footer replaced due to Continuing Review #3	09/04/14	N/A
12/08/14	Administrative Update: Nursing PES added	N/A	N/A
05/08/15	Protocol and Front Sheet replaced due to Amendment #37	04/23/15	N/A
05/11/15	Correction: AM #37 not ready for activation; previous Protocol and Front Sheet reposted	n/a	n/a
06/02/15	Protocol and Front Sheet replaced due to Amendment #37	04/23/15	N/A
07/08/15	Front Sheet replaced due to Amendment #38	07/08/15	N/A
Date Posted	**Revised Sections**	**IRB Approval Date**	**OnCore Version Date**
09/01/15	Study renewal / Consent Forms footer replaced due to Continuing Review #4	08/27/15	09/01/15
01/22/16	Front Sheet replaced due to Amendment #39	01/21/16	N/A
01/29/16	Alert Page replaced due to Amendment #40	01/28/16	N/A
08/09/16	Study renewal / Consent Forms footer replaced due to Continuing Review #5	08/04/16	08/08/16
Date Posted	**Revised Sections**	**Approved Date**	**Version Date (OnCore)**
01/05/17	Permanent Closure to New Accrual: objectives/accrual goal met (effective date:01/03/17; Amendment #41)	01/04/2017	N/A
07/24/17	Study renewal / Consent Forms footer replaced due to Continuing Review #6	06/08/2017	06/08/2017
09/12/17	Front Sheet replaced per AM #42	08/28/17	N/A
05/03/2018	Study renewal / Consent Forms footer replaced due to Continuing Review #7	04/24/2018	05/02/2018
04/08/2019	Study renewal/Consent Forms removed due to data analysis only per Continuing Review #8	04/08/2019	n/a

Protocol Version Date: March 6 2015

NCI Protocol #*:* N/A

Local Protocol #: 11-208

Title: A Phase II trial of cabozantinib in women with metastatic hormone-receptor-positive breast cancer with involvement of bone

Principal Investigator:

Name: Steven Isakoff, MD, PhD

Institution: Massachusetts General Hospital Cancer Center

Address: 55 Fruit Street, LHR 308

Phone: 617-726-4920

Fax:617-643-0589

Email: SIsakoff@mgh.harvard.edu

Coordinating Center:
Massachusetts General Hospital Cancer Center

Co-Investigators:
Monica Fornier
Memorial Sloan-Kettering Cancer Center, New York, NY, USA
fornierm@mskcc.org

Umar Mahmood MD, PhD
Associate Professor of Radiology,
Co-Director, Nuclear Medicine and Molecular Imaging
Massachusetts General Hospital

Jeffrey G. Supko PhD
Director, Clinical Pharmacology Lab
Massachusetts General Hospital
55 Fruit St., GRJ 1025

Alarice Lowe, M.D., Director
75 Francis St., MRB-315
Brigham and Women's Hospital
Boston, Massachusetts 02115

Statistician:
Dianne Finkelstein/Jackie Szymonifka

Institution: Massachusetts General Cancer Center

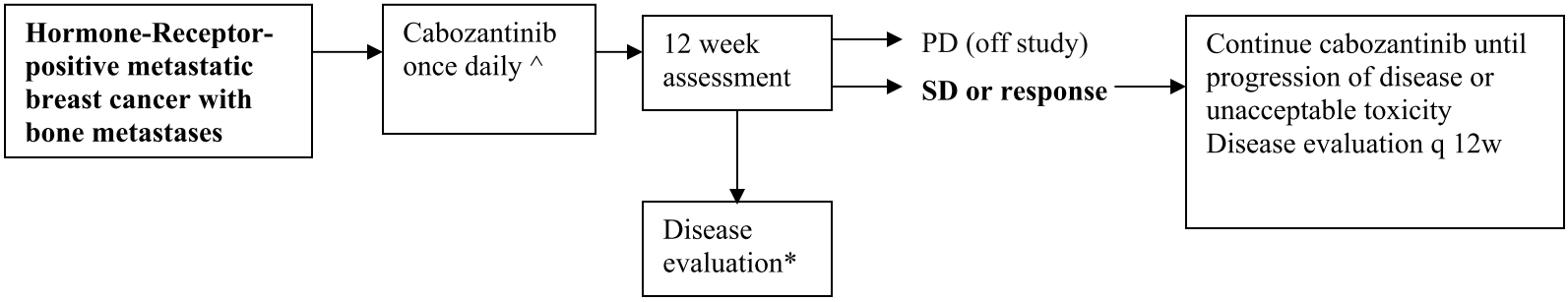
Study Coordinator: Lauren Kaplan

Responsible Research Nurse: Karleen Habin, RN

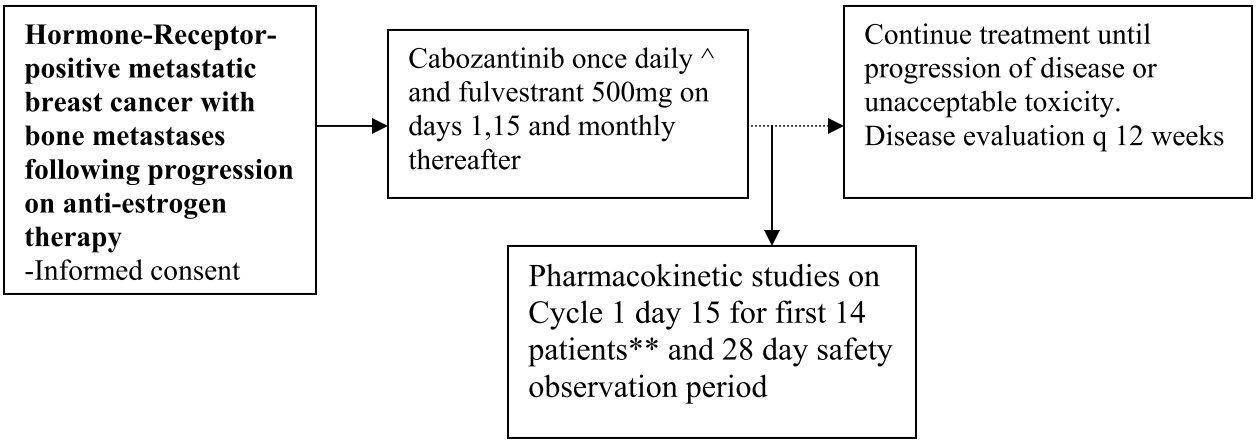
Responsible Data Manager: Lauren Kaplan

Agent: Cabozantinib (IND#72,596) - Exelixis

SCHEMA



Schema of Fulvestrant/Cabozantinib pilot cohort
N= 20 subjects



Adverse event and SAE reporting will begin from the time of the first dose of study treatment, through the study and until the final study visit.
^ Starting dose will be 40mg freebase weight
*Tumor response will be evaluated as outlined in Section 10.1 Radiological studies will be acceptable if performed within +/-4 days of 12 week intervals.
** PK patients to be accrued at MGH, DFCI or BIDMC only
PD = progressive disease
SD = stable disease

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is an open-label, single arm study of cabozantinib, a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGFR2, RET, and KIT, in patients with hormone-receptor-positive metastatic breast cancer with involvement of bone. 50 evaluable patients will be treated with Cabozantinib daily. The primary endpoint is the bone scan response rate. The study will undergo one interim analysis for futility when 17 evaluable patients have been accrued, dosed, and followed until the 12 week disease evaluation.

1.1.1 Pilot Fulvestrant/Cabozantinib Combination Cohort

A further 20 evaluable patients will be enrolled to a pilot cohort and treated with cabozantinib daily in combination with fulvestrant.
There will be a safety assessment after patients 9 through 14 (presuming all are evaluable for toxicity) have been enrolled. If no more than 2 DLTs have been observed among these 6 patients, (see section 2.8 for definitions) accrual will continue for the remaining 6 patients.

1.2 Primary Objective

- To evaluate the bone scan response rate in patients with hormone-receptor-positive breast cancer with bone metastases receiving cabozantinib.

(Bone scan response rate will be defined as the percentage of patients experiencing a complete resolution or significant improvement in bone scan, see section 10.1 as determined by both local institution and independent review facility, IRF)

1.3 Secondary Objectives

- To evaluate overall response rate (ORR) (defined as the percentage of patients experiencing a complete response or a partial response by mRECIST criteria per Appendix B)
- To evaluate Overall Survival
- To evaluate Progression Free Survival
- To evaluate the effects of cabozantinib on biochemical markers of bone turnover and tumor markers (for patients in main study only)
- To evaluate skeletal related event rates in study participants
- To evaluate FDG-PET response rate (for patients in main study only)

<u>Secondary Objectives of Pilot Combination Fulvestrant/Cabozantinib Cohort</u>

- To evaluate the safety and tolerability of concomitant administration of cabozantinib and fulvestrant in postmenopausal female patients with locally advanced or metastatic hormone receptor-positive breast cancer

- To make a preliminary assessment of the anti-tumor activity of cabozantinib in combination with fulvestrant in patients with metastatic hormone receptor-positive breast cancer

1.4 Exploratory Objective

- To identify surrogate biomarkers associated with clinical activity of cabozantinib (for patients in main study only)

2.BACKGROUND

2.1 Cabozantinib

A summary of cabozantinib clinical and nonclinical experience is contained in the Investigator's Brochure supplied by Exelixis. The Investigator's Brochure should be reviewed in conjunction with this study protocol.

Cabozantinib is a new chemical entity that inhibits multiple RTKs with growth-promoting and angiogenic properties. The primary targets of cabozantinib are RET, MET, VEGFR2/KDR, and KIT (Table 1)

Table 1: CABOZANTINIB IC_{50} Values in Biochemical, Enzymatic Assays

Kinase	IC_{50} (biochemical) [nM]
RET	3.8
MET	1.8
VEGFR2/KDR	0.035
KIT	4.6

IC_{50}, concentration required for 50 % target inhibition.

In vivo data from pharmacodynamic experiments show that cabozantinib inhibits key RTKs that promote tumor cell proliferation and/or angiogenesis (RET, MET, and VEGFR2). In xenograft

tumor models, cabozantinib inhibited VEGFR2 phosphorylation in lung tissue, with an ED_{50} of 26 mg/kg. The duration of action for cabozantinib was sustained with > 50 % inhibition observed 10-24 hours post-dose at a dose level of 100 mg/kg for all targets studied.

Treatment with cabozantinib shows rapid effects on the tumor endothelium, resulting in breakdown of the vasculature beginning 24 hours after administration of cabozantinib, thus suggesting potent anti-angiogenic effects of cabozantinib. These effects translate into significant tumor growth inhibition after cabozantinib treatment in multiple tumor models including human MTC, human breast cancer, human lung carcinoma, and rat glioblastoma. Overall, the data generated in vivo demonstrate that the target profile of cabozantinib translates to potent anti-angiogenic activity and potent anti-tumor efficacy.

2.2 Cabozantinib Nonclinical Toxicology

In nonclinical toxicity studies in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues. Histopathological changes present in bone and pancreas were considered secondary to cabozantinib administration. Cabozantinib was negative in *in vitro* bacterial, *in vitro* mammalian cell, and *in vivo* mammalian genotoxicity bioassays. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, and decreased fertility in male and female rats.

Safety pharmacology studies of cabozantinib administration did not demonstrate adverse effects on neurobehavioral or respiratory-system function in rats; furthermore, no significant changes in electrocardiographic parameters (including corrected

QT [QTc] interval) were observed by telemetry in dogs.

Cabozantinib was not an inhibitor of cytochrome P450 (CYP) 3A4 in vitro and is not predicted to have significant effects on CYP3A4 induction. Cabozantinib was shown to be an inhibitor of CYP2C8, CYP2C9*3, and CYP2C19 isozymes, in vitro and was also a substrate of CYP3A4-mediated metabolism. The mean plasma protein binding by cabozantinib in vitro was greater than 98%.

Additional toxicology information may be found in the Investigator's Brochure.

2.3 Clinical Experience

2.3.1 Clinical Summary

There are 13 clinical studies of cabozantinib for oncology indications including five Phase 1 studies, one Phase 1b/2 study, three Phase 2 studies and three Phase 3 studies for which safety and efficacy data are available. (as of Aug 2012) Details of all studies may be found in the Investigator's Brochure.

A pooled analysis of safety data in 1286 subjects with cancer treated with cabozantinib in company-sponsored open-label single agent studies (XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, XL184-301 [cabozantinib arm], and XL184-900) has been performed. The analysis includes the cabozantinib arm of placebo-controlled Phase 3 Study XL184-301 in subjects with MTC. The data cut-off for this analysis is 01 March 2012 for adverse events (AEs) and 01 June 2012 for serious AEs (SAEs). Separately, AE and SAE data are available for two ongoing company-sponsored single-agent studies: an ongoing hepatic impairment study (XL184-003; n=14) and a study conducted in Japanese subjects (XL184-014; n=14). In addition, AE and SAE data (cut-off dates 01 March 2012 and 01 June 2012, respectively) are available for 118 subjects in combination studies of cabozantinib with erlotinib (XL184-002; n=26) or temozolomide (TMZ) ± radiation therapy (XL184-202; n=92). Finally, SAEs through 01 June 2012 are reported for five ongoing investigator sponsored studies in 193 subjects.

A range of cabozantinib dose levels have been explored. In Phase 1 Study XL184-001, subjects were treated with cabozantinib at salt weight doses ranging from 0.08 to 11.52 mg/kg using an earlier PIB aqueous suspension formulation on an intermittent dosing schedule and from 25 mg (19.7 mg freebase equivalent weight) to 265 mg (209 mg freebase equivalent weight) in capsule form on a fixed daily dosing (qd) schedule. The single-agent maximum tolerated dose (MTD) of the capsule in a daily dosing schedule based on 28 days of dosing was determined to be 175 mg (L-malate salt weight; 138 mg freebase equivalent weight). The 175 mg dose level was evaluated in placebo-controlled Phase 3 Study XL184-301 in subjects with medullary thyroid cancer (MTC): dose modifications (reductions or interruptions) occurred frequently in the cabozantinib arm of this study. Lower doses of cabozantinib have been explored in other indications and two ongoing Phase 3 studies in prostate cancer are evaluating a capsule dose of 60 mg qd (expressed as freebase equivalent weight). Common to all approaches is the titration of the dose to individual patient tolerability.

2.3.2 **Clinical Safety Profile**

The severity of AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.3.3 Adverse Events

As of August 2012, data is available for 1286 subjects. Across company-sponsored open-label studies with single-agent cabozantinib, the most frequently (> 20% of subjects) observed AEs, regardless of causality, are

fatigue, diarrhea, decreased appetite, nausea, palmar-plantar erythrodysesthesia syndrome, weight decrease, vomiting, constipation, hypertension, dysgeusia, dysphonia, aspartate aminotransferase (AST) increases, and abdominal pain. Some of these events resulted in permanent study drug discontinuation, including fatigue, diarrhea, nausea, dysphonia, hypertension, rash, AST increased, ALT increased, and PPE syndrome. Effects that may be related to inhibition of VEGF, including hypertension, thromboembolic events, gastrointestinal (GI) perforation and hemorrhage, wound dehiscence, and proteinuria, have been observed in clinical studies with cabozantinib.

2.3.4 Serious Adverse Events

The most commonly reported SAEs (experienced by ≥1% of subjects), regardless of causality are pulmonary embolism, dehydration, pneumonia, diarrhea, vomiting, deep vein thrombosis, convusions, abdominal pain, nausea, dyspnea, mental status changes, hyponatremia, asthenia, renail failure, cnfusional state and urinary tract infection. A total of 52 deaths were reported within 30 days of the last dose of study drug; the majority was due to disease progression, and 5 deaths were assessed to be related to cabozantinib: GI hemorrhage (in one subject), PE (in two subjects), respiratory failure (in one subject), and hemoptysis (in one subject).

Detailed information regarding the safety profile of Cabozantinib from all studies may be found in the Investigator's Brochure.

2.3.5 Clinical Pharmacokinetics

Repeat daily dosing of cabozantinib capsules for 19 days resulted in an approximately 4- to 5-fold mean XL184 accumulation (based on AUC and C_{max} values) compared to a single dose administration; steady state is achieved by Day 15. The ratio of minimum to maximum plasma concentration (C_{min} to C_{max}) was 0.640 at steady-state, suggesting low fluctuation over the dosing interval. The effective plasma half-life for cabozantinib of 55 hrs from the PopPK analysis is a predictor of accumulation and time to steady state (by Day 15) following daily dosing. The terminal half-life of 120 hrs determined in single-dose studies is a predictor of drug washout following the last dose. Enterohepatic recirculation of cabozantinib may contribute to long terminal half-life estimates.

Plasma PK parameters for cabozantinib were comparable in subjects with advanced malignancies and healthy volunteers following single oral dose administration. Following oral capsule administration, the median time for cabozantinib to reach peak plasma concentrations

(T_{max}) ranged from 2 to 5 hours post-dose. A high-fat meal moderately increased C_{max} and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 175 mg oral cabozantinib dose.

Cabozantinib is highly protein bound in vitro in human plasma (> 99.9% at 0.2 and 1.0 μM, and 99.7% at 10 μM).

Cabozantinib at clinically-relevant steady-state plasma concentrations (≥125 mg/day daily for a minimum of 21 days) showed no statistically-significant effect on single-dose plasma PK exposure values (C_{max} and AUC) for the CYP2C8 substrate rosiglitazone in subjects with solid tumors. Thus, cabozantinib appears to present low potential for inhibiting the metabolism of concomitant medications that are substrates of CYP2C8 or CYP isozymes which have been shown to be less potently inhibited by cabozantinib in vitro (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4).

Cabozantinib is a substrate for CYP3A4 metabolism in vitro in NADPH-catalyzed human liver microsomal (HLM) incubations. Administration of strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance and increased single-dose plasma cabozantinib exposure (AUC range: 34-38% higher). In contrast, administration of strong CYP3A4 inducer rifampin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance and decreased single dose plasma cabozantinib exposure (AUC range: 76-77% lower). More details may be found in the Investigator's Brochure.

2.3.6 **Clinical Activity**

Preliminary clinical activity data are available for the Cabozantinib studies outlined in Table 2.4.

Table 2.4: XL184 Study Descriptions

Study Number	Study Description
XL184-001	A phase 1 dose escalation study of cabozantinib in adults with advanced solid malignancies. XL184-001 was designed primarily as a safety and PK study, and also included an exploratory endpoint of antitumor activity.
XL184-201	A phase 2 single-agent efficacy study of cabozantinib in subjects with progressive or recurrent glioblastoma

XL184-202	A Phase 1b/2 study designed to evaluate the safety and tolerability of XL184 and erlotinib administered in combination and to estimate the anti-tumor activity of cabozantinib with and without erlotinib in subjects with non-small cell lung cancer.
XL184-203	A phase 2 randomized discontinuation study of cabozantinib in subjects with either breast cancer, gastric/gastroesophageal junction adenocarcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, or small-cell lung cancer.

A total of 85 subjects with advanced solid tumors were enrolled in the XL184-001 study. Of the 85 subjects, 18 subjects experienced a tumor shrinkage of ≥ 30% including 17 (49%) of 35 subjects with medullary thyroid cancer with measurable disease. In the response evaluable subset of subjects with medullary thyroid cancer, 10 (29%) of 35 subjects had confirmed partial responses (cPRs). In addition, 15 subjects with medullary thyroid cancer had stable disease (SD) for at least 6 months.

In study XL184-201, a total of 196 subjects with relapsed Glioblastoma have been enrolled. At the dose of 125 mg (salt base strength) qd, cPRs were observed in 11 of 37 (30%) subjects without prior anti-angiogenic therapy, with a median duration of response of 5.1 months (range = 0.9+-6.7+). In subjects without prior anti-angiogenic therapy, progression-free survival at 6 months (PFS6) assessed by Kaplan-Meier estimate was 25%, with a 30% rate of censoring at the time of analysis. The median PFS interval was 16.0 and 7.9 weeks for anti-angiogenic naïve and anti-angiogenic pretreated subjects, respectively. At the dose of 175 mg (salt base strength) qd, cPRs were observed in 7 of 34 (21%) subjects without prior anti-angiogenic therapy, with a median duration of response of 2.9 months (range = 1.9-12.8). In subjects without prior anti-angiogenic therapy, PFS6 assessed by Kaplan-Meier estimate was 10%. The median PFS interval was 15.9 and 14.3 weeks for anti-angiogenic naïve and anti-angiogenic pretreated subjects, respectively.

In study XL184-202, a total of 65 subjects with NSCLC have been enrolled. As of 01 June 2010, the MTD determination of the combination of cabozantinib and erlotinib in the Phase 1 portion is ongoing. To date, 8 of 53 evaluable subjects treated in Phase 1 have experienced a ≥ 30%

decrease in the sum of tumor measurements as compared to baseline measurements. Confirmed partial response was achieved in 4 of 53 (8%) evaluable subjects.

In study XL184-203, a total of 198 subjects with advanced solid tumors have been enrolled. Six subjects achieved a cPR during the 12-week open-label Lead-In Stage, 2 with hepatocellular carcinoma [HCC], 2 with non-small-cell lung cancer [NSCLC], 1 with melanoma, 1 with prostate cancer). Of the 105 evaluable subjects (with minimum 12 weeks of follow-up) 43 achieved SD (11 with melanoma, 8 with NSCLC, 5 with pancreatic cancer, 5 with prostate cancer, 5 with HCC, 4 with gastric/gastroesophageal junction [GEJ] adenocarcinoma, 4 with ovarian cancer, 1 with small cell lung cancer [SCLC]). The overall disease control rates (PR + SD) at Week 12 were 88% in the HCC cohort, 86% in the ovarian cancer cohort, 67% in the prostate cancer cohort, 50% in the melanoma cohort, and 50% in the NSCLC cohort. Preliminary efficacy data for the cohort of subjects with castrate-resistant prostate cancer are provided in Section 2.6 below.

2.4 Breast Cancer

Breast cancer is the second-most common malignancy reported globally, next to skin cancer, resulting in nearly 411,000 deaths each year. Multimodality therapy, including surgery, radiation, anti-hormonal treatment, and cytotoxic agents, is the standard of care for advanced disease stage. The combination of HER2/neu, EGFR, or VEGFR targeted agents with cytotoxic chemotherapy, or their use as single agents, has resulted in clinical benefit. (1-3) However, treatment in metastatic breast cancer is still palliative in intent. New treatment modalities are needed to extend survival and improve cure rate in this disease. (4)

2.5 Rationale for evaluating cabozantinib in breast cancer

Hepatocyte growth factor (HGF) is an angiogenic cytokine that stimulates epithelial cell motility and invasion. Its receptor is a transmembrane tyrosine kinase encoded by the c-*met* protooncogene. Several experimental and clinical studies suggest the involvement of the MET oncogene in the onset and progression of breast carcinoma. (5, 6) Both MET and HGF overexpression in breast cancer have been associated with tumor invasiveness, metastasis, and reduced survival. (5, 7-10) There is evidence that tumor hypoxia promotes metastasis through the induction of MET overexpression by HIF-1alpha. (11) MET and its ligand HGF are therefore exciting potential drug targets for the treatment of breast cancer. (1, 12) In addition, nearly 50% of ductal infiltrating carcinomas have been noted to express MET by immunohistochemistry, and

of those approximately 70% are estrogen receptor (ER)-positive/ Progesterone receptor (PR)-negative while 30% were ER-positive/ PR-positive . (13)

Endocrine therapy is the main therapeutic option for patients with estrogen receptor ER-positive breast cancer. Resistance to this treatment is often associated with estrogen-independent activation of ER. In ER-positive breast cancer cells, activation of the receptor tyrosine kinase RET (REarranged during Transfection) by its ligand results in increased ER phosphorylation on Ser118 and Ser167 and estrogen-independent activation of ER transcriptional activity. (14) Expression of RET protein is significantly associated with ER-positive tumors and with the development of recurrent disease after adjuvant tamoxifen treatment,(14-16) thus along with MET, co-targeting RET may be a potentially important therapeutic target in ER-positive and hormone-resistant breast cancers. (14)

Twenty one patients with measurable metastatic breast cancer were included in the Phase II Randomized Discontinuation Study of cabozantinib in Subjects with Advanced Solid Tumors. This was arguably a particularly poor prognosis metastatic breast cancer patient group due to the requirement for measurable disease on the study however, 3 of the twelve patients for whom data are available (as of September 2010) experienced a partial response in visceral disease-sites with cabozantinib treatment. All responders had ER+/PR+ disease and the lone patient with bone metastases visualized at baseline experienced a dramatic bone scan response at 6 weeks that was accompanied by an improvement in pain scores and 29% shrinkage in target lesions. This particular patient previously received several lines of hormonal therapies for the treatment of her metastatic disease.

2.6 Rationale for Cabozantinib Dose Selection

A cabozantinib starting dose of 100 mg qd has been studied in 171 CRPC subjects enrolled to the Phase 2 XL184-203 RDT. Despite relatively high rates of cabozantinib dose reductions to the next lowest dose of 60 mg qd within the first 12 weeks of therapy (51%), this starting dose resulted in high rates of pain relief, bone scan improvement, and overall disease control.

Cabozantinib has been extensively studied in the treatment of metastatic castrate-resistant prostate cancer where many responses have been observed but adverse events caused frequent dose reductions. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases was therefore performed. Cabozantinib 40 mg daily was associated with a high rate of bone scan response and better tolerability than previously reported for higher doses of cabozantinib. These observations informed the design of phase III studies of

cabozantinib in metastatic castration resistant prostate cancer. (Lee RJ et al, Clin Cancer Res 2013)

Preliminary results from the first 53 evaluable patients with metastatic breast cancer treated on this protocol with single agent cabozantinib at a starting dose of either 100 or 60mg:

100% of patients required a dose reduction or interruption from the starting dose of 100mg and 86% of patients required a dose reduction or interruption from the starting dose of 60mg. Despite this, preliminary results suggest that the study will still reach its primary endpoint of >30% of patients experiencing a bone scan response with the treatment.

As such, this study will adopt a starting cabozantinib dose of 40 mg qd. The goal of this regimen is to improve the overall tolerability of cabozantinib while maintaining efficacy.

2.7 Rationale for Pilot Fulvestrant/Cabozantinib Combination cohort

Endocrine therapy is the main therapeutic option for patients with estrogen receptor (ER)-positive breast cancer. A number of endocrine therapeutic options have been developed for the treatment of locally advanced or metastatic breast cancer including aromatase inhibitors (AIs) that reduce peripheral estrogen synthesis and fulvestrant which is an ER antagonist. Fulvestrant (Faslodex®) is approved in postmenopausal hormone receptor-positive metastatic breast cancer patients for disease relapse after antiestrogen therapy. Fulvestrant 250 mg monthly and exemestane were compared in a double blind placebo controlled phase III trial in 693 postmenopausal women with hormone receptor positive breast cancer after recurrence or progression on a non-steroidal AI (17). No difference in progression-free survival (PFS) (median 3.7 months in both arms), response rate (7.4% vs. 6.7%, respectively) or clinical benefit rate (32.2% vs. 31.5%) was observed. Higher dose of fulvestrant (500 mg monthly) has been compared to 250 mg monthly in patients who experienced progression after prior endocrine therapy. High dose fulvestrant (500 mg) significantly prolonged PFS compared to the 250 mg (median PFS 6.5 vs. 5.5 months; HR 0.80; 95%CI: 0.68 – 0.98; p .006) (18). Fulvestrant 500 mg is the dose that has been approved in both US and Europe for hormone-receptor-positive metastatic breast cancer following disease relapse after anti-estrogen therapy.

Acquired resistance to therapy is a common problem in the clinic and often associated with estrogen-independent activation of ER. In addition to the aforementioned preclinical work describing a role for inhibition of RET to potentially overcome resistance in ER-positive breast cancer cells, (14-16) other preclinical work has shown that fulvestrant resistant cell lines have developed upregulated cMet expression and that the combination of multitargeted tyrosine

kinase inhibition (TKI) and fulvestrant enhances antitumor effect. (19, 20) thus co-targeting RET and MET in combination with fulvestrant may be a potentially important therapeutic target in ER-positive and hormone-resistant breast cancers. (14)

In routine clinical practice, patients with metastatic hormone-receptor-positive breast cancer are treated with endocrine therapies for as long as possible to spare them the toxicities of chemotherapy. Resistance to such therapies inevitably develops and current research is focusing on combinatorial approaches to enhance and prolong sensitivity to endocrine agents. (21) In addition to the preclinical studies mentioned above, there are now some early clinical trials studying the combination of endocrine therapies with VEGF inhibitors or multitargeted TKI inhibitors. (22, 23) Therefore, when accrual of 52 evaluable patients is complete there will be an expansion cohort for another 20 evaluable patients looking at the combination of cabozantinib with fulvestrant. This cohort will be limited to post-menopausal women with hormone-receptor positive metastatic breast cancer that has progressed on prior anti-estrogen therapy. Subjects shall receive fulvestrant at 500mg (500 mg intramuscularly [IM] on Days 1 and 15 of Cycle 1 and on Day 1 of every cycle thereafter as per (18, 24) with cabozantinib daily.

Although there is no previous clinical experience on the use of fulvestrant in combination with cabozantinib, based on the pharmacologic properties of these drugs there is no expected alteration of cabozantinib metabolism by fulvestrant. Fulvestrant has no known drug-drug interactions. (see Section 7.2.1 for further details) Furthermore, these drugs are generally very well tolerated with non-overlapping toxicities. Fulvestrant was chosen as an endocrine partner rather than aromatase inhibitors (AIs) for this cohort due to the scientific rationale outlined above, it's equivalent efficacy and preferred side-effect profile. Results from the analysis of PK samples obtained from the first 8 patients treated on this protocol during the third week of treatment with cabozantinib 60mg daily and fulvestrant, found the mean +/- steady-state trough concentration of cabozantinib in the plasma was 1245 +/-306ng/ml and the mean apparent oral clearance (CL/F) was 2.45 +/- 0.65 L/h. The steady-state trough concentrations are approximately 2-fold higher than expected based upon extrapolations from published data for patients receiving the 138mg (free base) daily dose. Although metabolism mediated by CYP3A4 appears to be an important route of elimination for cabozantinib, it is highly unlikely that the higher than anticipated steady-state plasma concentrations of the drug observed in these patients is attributable to the coadministration of fulvestrant. There are no known drug-drug interactions involving fulvestrant as it has been shown that therapeutic doses have no inhibitory effects on CYP3A4 or alter blood levels of other drugs metabolized by that enzyme. It is possible that these results are due to high intersubject variability in exposure in a very small sample size, or possibly

gender related differences in exposure. (the oral clearance value provided in the label for cabozantinib (4.4 L/Hr) was based on a population PK model estimate for males). While this gender difference was not considered large enough to merit dose adjustment per the label, it could nonetheless contribute to the higher exposure seen in this study which enrolled all females.

Accrual was halted following the observation of 3 DLTs during the first 28 days of treatment in the first 8 patients treated with cabozantinib and fulvestrant. A teleconference call was held with all investigators. It was strongly felt that the DLTs observed are commonly associated with single agent cabozantinib and that they reflected an intolerable dose of cabozantinib rather than any deleterious interaction between fulvestrant and cabozantinib. The trial was closed to accrual with plan to reopen using a starting dose of cabozantinib 40mg. As an extra safety precaution, accrual will be paused when the next 6 evaluable patients(patients 9 through 14 in this cohort) have received first doses of cabozantinib and fulvestrant. These 6 patients will observed for 4 weeks and assessed for DLTs (defined below).

A teleconference call with all investigators will be held at the end of this period to discuss any unexpected SAEs that may have been observed

Accrual will be suspended either temporarily or permanently if, in the opinion of the principal investigator, any such SAE warrants further evaluation or discontinuation of the cohort. Ongoing accrual to this cohort will be stopped permanently if more than 2 patients experience a DLT. If DLTs are observed in 2 or fewer patients, accrual will continue.

2.8 Definition of Dose-Limiting Toxicity

All adverse events will be reported, with severity assessed according to the NCI CTCAE v4.0.Dose limiting toxicity (DLT) refers to both non-hematologic and hematologic toxicities experience during the first cycle (i.e., first 4 weeks) of treatment.

A DLT will be defined as any of the following assessed by the investigator to be possibly related to cabozantinib occurring during cycle 1 (for the first 8 patients in the fulvestrant/Cabozantinib pilot cohort:

1. Any AE that results in a dose reduction during the DLT evaluation period
2. Non-Hematologic Toxicity
    i. Any Grade 3 or 4 event, excluding:
        a. Grade 3 nausea and/or vomiting controlled with supportive measures within 24 hours,
        b. Grade 3 diarrhea controlled with supportive measures within 24 hours,
        c. Grade 3 fatigue that resolves within 24 hours

d. Grade 3 constipation controlled with supportive measures within 24 hours,
e. Grade 3 hypophosphatemia
f. Grade 3 hyponatremia
g. Grade 3 hypomagnesemia
h. Grade 3 hypokalemia
i. Grade 3 hepatic transaminase (ALT or AST)
j. Grade 3 hypertension controlled with medical management

Note: For patients with Grade 1 hepatic transaminase at baseline as a result of liver or bone metastases, hepatic transaminase ≥7.5 x the upper limit of normal (ULN) will be considered a DLT.

3. Hematologic Toxicity
    i. Grade 4 neutropenia of > 7 day's duration
    ii. Febrile neutropenia (a disorder characterized by an ANC < 1000/mm3 and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of >/= 38 degrees C (100.4 degrees F) for mor than one hour
    iii. Dose delay of greater than 3 weeks (21 days) due to failure to recover counts.
    iv. Grade 4 thrombocytopenia or bleeding associated with grade 3 thrombocytopenia
    v. Requirement for repeated blood transfusion within 4-6 weeks

4. Inability to take 75% or more of the planned dose in Cycle 1 due to treatment-related adverse effects
5. Any study treatment related death

6. Management and dose modifications associated with the above adverse events are outlined in Section 6.3

2.9 Correlative Studies Background

Rationale for evaluating bone scan response as primary endpoint

Overall, bone is the most common site to which breast cancer metastasizes, and the site of first metastasis in approximately 50% of patients with breast cancer. Up to 75% of patients with metastatic breast cancer will develop bone metastases during the course of their disease and this number is even higher among those with hormone-receptor positive disease. (25-27) For 20–25% of patients with metastatic breast cancer, especially those with hormone sensitive disease, bone will be their only site of metastatic involvement. (28) Bone metastases associated with breast cancer are osteolytic and/or osteoblastic and are associated with considerable morbidity including; hypercalcemia, increased fracture risk, need for surgery or radiotherapy and spinal cord compression. (26, 29)

Metastatic bone lesions from cancer as imaged on bone scan, FDG-PET scan or plain films are not considered 'measurable' by the widely accepted RECIST criteria v1.1. (30) Because of this, patients with bone-only or bone-predominant metastatic breast cancer without measurable disease have been excluded from the vast majority of clinical trials which include response measurements as a primary endpoint. Such patients are common in the breast clinic and there is an unmet need to evaluate novel agents that may effectively treat their metastatic disease burden in bone as well as soft tissue sites. In 2004 the University of Texas MD Anderson Cancer Center developed a set of criteria for the assessment of bone metastases and included quantitative and qualitative assessments of the behavior of bone metastases as assessed by isotope bone scans, CT scans, or MRI. (31) The MD Anderson criteria can allow more bone lesions to be considered measurable disease than does the RECIST 1.1 system by allowing physical measurement of well-defined bone lesions regardless of soft tissue extension, by allowing regimented subjective assessment of ill-defined lesions and by taking into account characteristic behaviors such as the development of healing sclerosis. In a study comparing the MDA criteria and two other criteria used internationally to assess response in bone, (the UICC and WHO criteria) in 41 breast cancer patient with bone-only metastases, the MDA criteria were shown to better differentiate responders to chemotherapy from nonresponders and were the only set of criteria to correspond to progression free survival. (32). Isotope bone scans (also called Technetium bone scans or skeletal scintigraphy, SS) are the most commonly used means of detecting bone metastases as they are widely available and can produce rapid whole-body images at a reasonable cost. (31, 33) SS visualizes increases in osteoblastic activity and skeletal vascularity. According the MDA criteria, complete response can be defined as the disappearance of abnormal tracer uptake on

skeletal scintigraphy (SS) and partial response (PR) as ≥ 50% subjective decrease in tracer uptake on SS. Progressive disease was defined by MDA criteria as a ≥ 25% subjective increase in tracer uptake on SS or the development of new metastases. A caveat to the PR designation involves the osteoblastic flare phenomenon. Interval visualization of sclerotic lesions of lytic lesions with sclerotic rims, in the setting of other signs of partial response does not indicate disease progression but the healing of previously inconspicuous lesions. Osteoblastic flare cannot be diagnosed if any preexisting lesions show signs of progression (eg enlargement of lytic lesions, development of new lytic lesions).

Integrated PET/CT has become increasingly accepted for routine surveillance and follow up of breast cancer patients with and without bone metastases. (34, 35) Several studies suggest that decreases in serial FDG PET may predict response duration and time to progression in bone-dominant breast cancer. (34, 36) Metabolic imaging criteria can allow bone metastases to be measured in the absence of anatomic change by assessing tumor metabolism. The Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria have been proposed to standardize assessment of tumor response using PET/CT. (see table 3, Costelloe et al (37)

Among the castrate-resistant prostate cancer cohort in the phase II randomized discontinuation study of cabozantinib, dramatic decreases in radiotracer uptake on bone scans have been observed in 19 out of 20 subjects who had bone metastases visualized on bone scans at baseline. (Includes patients with evaluable data as of Sept 2010) Decreases in radiotracer uptake have been associated with the following: (1) decreases in soft-tissue lesion measurements; (2) prompt reductions in pain and narcotic use, including subjects who have completely discontinued narcotic use; (3) substantial decreases in total alkaline phosphatase levels, following initial rises, for subjects with elevated alkaline phosphatase at baseline; (4) increases in hemoglobin and hematocrit, for subjects with anemia at baseline; and (5) varying PSA changes (both increases and decreases) which have not consistently correlated with these other parameters. In view of the striking bone scan responses observed in the ongoing Phase II randomized discontinuation study as well as the clinical availability and usefulness of bone scans for the evaluation of bone metastases in metastatic breast cancer, bone scan response has been chosen as the primary endpoint of this study. Although this is a novel primary endpoint for a breast cancer trial, we believe it is a clinically relevant one. Taking into consideration the similarities of bone involvement between prostate cancer and breast cancer and the observed clinical activity mentioned above, we hypothesize that cabozantinib will achieve a bone scan response rate of at least 30% on this trial and that such an intervention would be highly worthy of future study.

This study is designed for patients with metastatic breast cancer to bone. To assess the activity of cabozantinib in this population, tumor response will be assessed approximately every 12 weeks from first dose of study drug. Patients will be assessed by isotope bone scan alone and whole body FDGPET/CT with contrast. Bone scan response will be defined as outlined in section 10.1 and will be evaluated at the local institution and by independent review facility. The bone scan response endpoint will be evaluated along with changes in soft-tissue measurements among patients with measurable disease, measures of clinical benefit, and markers of bone metabolism.

The effects of cabozantinib on FDG-PET appearances have not previously been assessed therefore evaluation of FDG-PET-CT response is a secondary endpoint of the study. All radiology will be read at home institution and also sent to independent review facility. (MEDQIA)

Patients participating in the pilot combination fulvestrant/cabozantinib study will be followed with routine bone scan and CT only.

Bone turnover markers

Skeletal metastases are difficult to diagnose non-radiologically and treatment may be difficult to follow clinically. Recent developments suggest that biochemical markers of bone remodeling, such the serum bone formation marker bone-specific alkaline phosphatase (a marker of osteoblast function), hold great promise as clinical tools for the management of patients with metastatic bone disease. (38) Bone metastases in breast cancer can be characterized by elevated bone turnover markers such as the urinary-N-telopeptide (NTX) /creatinine ratio. Patients with elevated levels of uNTx/Cr are at increased risk for skeletal complications, disease progression and death. (39-41) Conversely, normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors. (42) Changes in serum N telopeptide, C telopeptide, Procollagen type 1 N-terminal peptide and bone alkaline phosphatase will be recorded and correlated with responses observed in this study. Most patients on this study will likely be receiving concomitant treatment with either bisphosphonates or denosumab for the prevention of skeletal related events. These agents themselves have been shown to reduce bone metabolites by approximately 65% however, in analyses of men with metastatic prostate cancer, cabozantinib decreased collagen N-telopeptide by a median of about 70% in both bisphosphonate-naive and bisphosphonate treated subjects. Therefore information about bisphosphonate/denosumab use at baseline will be collected and bone marker analyses will be conducted on overall study population as well as subgroups based on use of bone-directed therapy.

Circulating Tumor Cells

There is a growing literature on the useful association of trends in detectable circulating tumor cells (CTCs) in breast cancer and response to therapy. (43) CTCs will be collected at baseline and with each cycle from participants in the cabozantinib/fulvestrant cohort for exploratory analyses.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. The subject must have clear evidence of metastases to bone on isotope bone scan at screening, with or without soft tissue metastases. In subjects with bone-only disease, at least two bone lesions must be evident on baseline imaging that are not within a previously irradiated field.

2. The subject must have histologically or cytologically confirmed metastatic ER+ and/or PR+ and HER2 negative breast cancer. (Stains may be performed on either primary or metastatic tumor samples, ER and PR assays will be considered positive if there are at least 1% positive tumor nuclei in the sample as per ASCO/CAP Guidelines (44), HER2 negative as per ASCO/CAP Guidelines. (45)

3. The subject must have progressive disease following at least one prior line of hormonal or chemo- therapy for treatment of their metastatic disease. (see specific additional criteria for patients in the fulvestrant/cabozantinib cohort)

4. The subject must have discontinued any endocrine therapy for at least 2 weeks before the first dose of study treatment. In the cases of fulvestrant and leuprolide, these must be discontinued for at least 4 weeks before the first dose of study treatment.

5. The subject has recovered to baseline or CTCAE $\leq$ Grade 1 from toxicities related to prior treatment, except alopecia, lymphopenia, other non-clinically significant AEs.

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

7. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix D)

8. The subject has an estimated life expectancy of more than three months.

9. The subject has organ and marrow function as follows:

a. Absolute neutrophil count (ANC) ≥ 1500/mm^3, without colony stimulating factor support.
b. Platelets ≥ 100,000/mm^3
c. Hemoglobin ≥ 9 g/dL, without ongoing chronic blood transfusion or colony stimulating factor support to maintain normal levels. Principal Investigator approval is required. (Limited RBC transfusion is allowed for an acute change in hemoglobin)
d. Total bilirubin ≤ 1.5 × the upper limit of normal. For subjects with known Gilbert's disease, ≤ 3 mg/dl. Alk phosphatase ≤ 5 x upper limit of normal.
e. Serum albumin ≥ 2.8 g/dL.
f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 50 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:

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

   Female: Multiply above result by 0.85

g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × the upper limit of normal if no liver involvement, or ≤ 5 × the upper limit of normal with liver involvement.
h. Lipase < 1.5 times the upper limit of normal
i. Urine protein/creatinine ratio (UPCR) ≤ 1.
j. Serum phosphorus, calcium, magnesium and potassium ≥ lower limit of normal

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

11. Sexually active fertile subjects (male and female), and their partners, must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study drug(s).

12. Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, or ovarian suppression or other reasons.

13. The subject is able to lie flat for up to 45 minutes for imaging studies.

3.2 Exclusion Criteria

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

1. The subject has a corrected QT interval (QTc) >500 ms at screening or has a history of long QT syndrome.

2. The subject has experienced clinically-significant hematemesis or hemoptysis of > 0.5 teaspoon of red blood, or other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment.

3. The subject has cavitating pulmonary lesion(s) or a pulmonary lesion abutting or encasing a major blood vessel.

4. The subject has tumor in contact with, invading or encasing any major blood vessels.

5. The subject has received systemic chemotherapy (including investigational agents) within 4 weeks, or biological agents (antibodies, immune modulators, cytokines, or vaccines*) within 6 weeks, or hormonal anticancer therapy within 2 weeks before the first dose of study treatment. (within 4 weeks in the case of fulvestrant) (* vaccines, such as flu shot or, pneumovax are not exclusions)

6. The subject has received small-molecular kinase inhibitors or any other type of investigational agent within 4 weeks before the first dose of study treatment or 5 half-lives of the compound or active metabolite, whichever is shorter.
7. The subject has received radiation therapy:
    a. to the thoracic cavity or gastrointestinal tract within 3 months of the first dose of study treatment.
    b. to bone or brain metastasis within 14 days of the first dose of study treatment
    c. to any other site(s) within 28 days of the first dose of study treatment

8. The subject has started treatment with drugs used to control loss of bone mass (eg, bisphosphonates or denosumab) within 4 weeks prior to the first dose of study treatment.

9. The subject has untreated, symptomatic or uncontrolled brain metastasis requiring current treatment including steroids and anti-convulsants. Neurosurgical resection of brain metastasis or brain biopsy is permitted if completed at least 3 months before the first dose of study treatment.

10. The subject has prothrombin time/International Normalized Ratio (PT/INR) or partial thromboplastin time (PTT) test results at screening ≥ 1.3 x the laboratory upper limit of normal.

11. The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or coumadin-related agents, thrombin or FXa inhibitors, and antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic Low Molecular Weight Heparin (LMWH) are permitted. Therapeutic anticoagulation with LMWHs may be allowed in certain circumstances as outlined as outlined in section 6.3.5.

12. The subject has experienced any of the following within 3 months before the first dose of study treatment:
    a. clinically-significant hematemesis or lower gastrointestinal bleeding
    b. hemoptysis of > 0.5 teaspoon of red blood
    c. any other signs indicative of pulmonary hemorrhage

13. The subject has uncontrolled or significant intercurrent illness including, but not limited to, the following conditions:
    - Cardiovascular disorders such as symptomatic congestive heart failure (CHF), uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening), unstable angina pectoris, clinically-significant cardiac arrhythmias, history of stroke (including TIA, or other ischemic event) within 6 months of study treatment, myocardial infarction within 6 months of study treatment, history of thromboembolic event requiring therapeutic anticoagulation within 6 months of study treatment or main portal vein or vena cava thrombosis or occlusion. (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)

    a. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
        i. Any of the following at the time of screening
            - intra-abdominal tumor/metastases invading GI mucosa
            - active peptic ulcer disease,
            - inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
        ii. Any of the following within 6 months before the first dose of study treatment:
            (1) history of abdominal fistula
            (2) gastrointestinal perforation
            (3) bowel obstruction or gastric outlet obstruction
            (4) intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more that 6 months ago.
        iii. GI surgery (particularly when associated with delayed or incomplete healing) within 28 days. Note: Complete healing following abdominal surgery must be confirmed prior to initiating treatment with cabozantinib even if surgery occurred more that 28 days ago.

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

c. Other clinically significant disorders such as:

i. active infection requiring systemic treatment

ii. serious non-healing wound/ulcer/bone fracture

iii. history of organ transplant

iv. concurrent uncompensated hypothyroidism or thyroid dysfunction

v. history of major surgery within 4 weeks or minor surgical procedures within 1 week before randomization

12. The subject is unable to swallow capsules or tablets.

13. The subject is pregnant or breastfeeding.

14. The subject has a previously-identified allergy or hypersensitivity to components of the study treatment formulation.

15. The subject requires chronic concomitant treatment of strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).

16. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

17. The subject has had another diagnosis of malignancy, requiring systemic treatment, within the last two years, unless non-melanoma skin cancer, in-situ carcinoma of the cervix, or superficial bladder cancer.

3.2.1 Additional Inclusion & Exclusion Criteria for patients in Combination Fulvestrant/Cabozantinib cohort

Inclusion Criteria

1. Subject is post-menopausal defined as age over 60 or status post bilateral oopherectomy. In subjects aged 50-60 years they shall be considered eligible if FSH/LH and estradiol is within institutional post-menopausal range at time of study entry.

2. Subject has hormone-receptor positive metastatic breast cancer with disease progression following antiestrogen therapy.

Exclusion Criteria

1. Subject has had prior progression on treatment with fulvestrant. (Prior adjuvant treatment or brief exposure in the advanced setting is allowed.)

2. Subject has received more than 1 prior line of chemotherapy treatment for metastatic breast cancer

3. Subject has had prior treatment with Cabozantinib

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Both men and women and members of all races and ethnic groups are eligible for the main study For the combination fulvestrant/cabozantinib cohort, only post-menopausal women are eligible.

4. REGISTRATION PROCEDURES

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

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

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

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

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

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

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

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

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the Massachusetts General Hospital Cancer Center by the Study Coordinator, Elizabeth Tripp. All external sites should call Elizabeth Tripp at 617-726-1634 to verify treatment availability. Refer to Section 4.4 for documentation requirements for registration.

Following registration, participants should begin protocol treatment within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Study Coordinator should be notified of participant status changes as soon as possible.

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

4.4 Registration Process for Other Participating Institutions

To register a participant, the following documents should be completed by the research nurse or data manager and faxed to (fax # 617-726-0792) or emailed to Elizabeth Tripp at ETripp@mgh.harvard.edu:

- Source documentation confirming eligibility:
  - Pathology report confirming histologically or cytologically confirmed ER+ and/or PR+ and HER2 negative breast cancer
  - Radiology report from bone scan documenting clear evidence of bone metastases
  - Clinic note documenting physical exam, height, weight, vital signs, ECOG performance status
  - Applicable clinic notes confirming all other eligibility criteria
- Copy of required laboratory tests:
  - Hematology including Complete Blood Count with Differential, Platelets
  - Serum chemistry panel including albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, phosphorus, sodium, total bilirubin, total protein
  - Serum or urine pregnancy test for women of child-bearing potential
  - PT/INR or PTT
  - TSH
  - Tumor markers CA 27.29 or CA 15.3
- Signed study consent form
- HIPAA authorization form
- Eligibility Checklist

The research nurse or data manager at the participating site will then call 617-726-1634 or email the Study Coordinator, Elizabeth Tripp, at ETripp@mgh.harvard.edu to verify eligibility. To complete the registration process, the Coordinator will:

- Register the participant on the study with the QACT
- Fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site

- Call the research nurse or data manager at the participating site and verbally confirm registration

Note: Registration and randomization with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

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

Subjects will receive cabozantinib orally administered daily and continuously. Dosing will begin at 40 mg cabozantinib freebase weight per day taken orally for all patients with dosing delays/dose modifications as outlined in Section 6.

Subjects will be provided with a sufficient supply of study treatment and instructions for taking the study treatment on days without scheduled clinic visits. After fasting (with exception of water) for 2 hours, participants will take study treatment daily each morning with a full glass of water (minimum of 8 oz/ 240 mL) and continue to fast for 1 hour after each dose of study treatment. Participants should record dosing time and doses taken in a study drug dosing diary while on study treatment. If doses are withheld, the original schedule of assessments should be maintained when cabozantinib is restarted. The participant should be instructed to not make up the missed doses and to maintain the planned dosing schedule. Participants must be instructed to not make up missed doses that are vomited

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

A cycle length will be defined as 21 days (3 weeks) in the main study

For the fulvestrant/cabozantinib combination cohort a cycle length will be defined as 28 days. Dosing should be on Days 1 and 15 of Cycle 1 and on Day 1 of every cycle thereafter.

5.1 Pre-treatment Criteria

Cycle 1, Day 1: The following pre-treatment criteria must be met in order to begin study treatment on Cycle 1 Day 1: Absolute neutrophil count (ANC) ≥ 1500/mm3; platelets ≥ 100,000/mm3; hemoglobin ≥ 9 g/dL; total bilirubin ≤ 1.5 × the upper limit of normal; serum albumin ≥ 2.8 g/dL; serum creatinine ≤ 1.5 × the upper limit of normal or calculated creatinine clearance ≥ 50 mL/min or GFR > 40 ml/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × the upper limit of normal if no liver involvement; or ≤ 5 × the upper limit of normal with liver involvement; urine protein/creatinine ratio (UPCR) ≤ 1; serum phosphorus ≥ lower limit of normal.

5.2 Agent Administration

5.2.1 Cabozantinib

Cabozantinib will be supplied as 20 mg tablets. The cabozantinib tablet components are presented in Section 7. For a description of the salt and freebase equivalent weights of doses and capsule strengths mentioned in this study, see **Appendix A**.

Fulvestrant is supplied in sterile single-patient prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. Refer to the fulvestrant (e.g., FASLODEX) Package Insert for details on the storage of fulvestrant. Patients will receive fulvestrant 500 mg, administered intramuscularly in the buttocks slowly (1−2 minutes per injection) as two 5-mL injections (one in each buttock), in the clinic on Days 1 and 15 of Cycle 1. For subsequent cycles patients will receive fulvestrant via intramuscular injections as described above in the clinic on Day 1 of each cycle.

5.2.2 **Dose, Schedule and Route**

Participants will receive cabozantinib orally administered daily at the assigned starting dose of 40 mg cabozantinib freebase weight per day taken orally.

For the fulvestrant/cabozantinib combination cohort dosing will begin with fulvestrant 500mg IM on days one and 15 of Cycle 1 and on day 1 of each subsequent cycle.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 **Anticancer Therapy**

If a participant requires additional systemic anticancer treatment, study treatment must be discontinued. These treatments include, but are not restricted to the following:

- Chemotherapy
- Radiopharmaceuticals
- Steroids (not including physiological replacement doses of steroids, equivalent to ≤ 10 mg/day prednisone, or megestrol acetate used to treat constitutional symptoms)
- Endocrine therapy for breast cancer (eg, tamoxifen, aromatase inhibitors)
- Radiation therapy

5.3.2 Other Medications

If the participant must use other concomitant medications during the study (including vitamins, herbal and nutritional supplements, and over-the-counter medications), it is the responsibility of the principal investigator (PI) to ensure that details regarding the medication are documented.

At the discretion of the investigator and after the onset of symptoms, treatment (or prophylaxis) with anti-emetic and anti-diarrheal medications may be undertaken per standard clinical practice.

Treatment with denosumab or a bisphosphonate is allowed provided treatment was initiated more then 4 weeks prior to Cycle 1 Day 1.

Colony stimulating factors (eg, erythropoietin and granulocyte colony-stimulating factors) administered as dictated by standard practice are acceptable while the participant is enrolled in the study.

Pain medications, transfusions, short-term systemic steroid treatment, and other supportive measures should be utilized as dictated by standard clinical practice while the participant is enrolled in the study.

No concurrent investigational agents are permitted.

5.3.3 Potential Drug Interactions

The current available data suggest that cabozantinib: (1) is not anticipated to markedly inhibit CYP enzymes in the clinic; (2) is unlikely to induce CYP enzymes in the clinic; (3) is a substrate

for CYP3A4; and (4) does appear to have the potential to inhibit the P-gp transport activity but is not a substrate of P-gp.

Drugs such as proton pump inhibitors (PPIs) and H2 antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs, and H2 antagonists may decrease cabozantinib exposure and its effectiveness in vivo, resulting in clinically significant drug interactions. No effect of gastric pH modifiers on cabozantinib exposure was observed in dogs and no effect of PPIs and H2 blockers on cabozantinib PK was seen in the population PK analyses. However, a clinical study has not been done to assess the effect of gastric pH modifying drugs. Therefore, the use of PPIs (eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H2 antagonists (eg, ranitidine, famotidine, and nizatidine) is discouraged while taking cabozantinib. If antacids are not adequate, the use of H2 blockers is preferred over PPIs (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4-mediated metabolism of cabozantinib). Antacids, H2 blockers, or 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.

Concomitant medications that are highly protein bound or that are inhibitors of the CYP3A4 pathway should be used with caution. Chronic use of strong CYP3A4 inducers such as rifampin, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, St. John's wort, and troglitazone should be avoided. In addition, strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Patients should be told that cabozantinib should not be taken with food, and should be taken with a full glass of water on an empty stomach; patients should fast at least 2 hours before and 1 hour after taking cabozantinib.

5.4 There are no known drug interactions with fulvestrant. Duration of Therapy

5.4.1 Initial therapy

Treatment may continue until one of the following criteria applies:

- Clinical disease progression as defined in Section 10.1, or
- Intercurrent illness that prevents further administration of treatment, or
- Unacceptable adverse event(s), or
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements, or
- Participant decides to withdraw from the study, or

- Changes in the participant's condition rendering the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Participants will be followed for at least 30 days after last dose of study drug. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Survival status for each participant will be assessed every six months for the first two years that the participant comes off study treatment and annually thereafter for up to five years.

5.6 Criteria for Removal from Study

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

In addition, any of the following conditions require withdrawal of the participant from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the participant’s withdrawal from treatment
- Necessity for treatment with other investigational drug or other anticancer medications prohibited by protocol
- Participation in another clinical study using an investigational agent
- Request by regulatory agencies for termination of treatment of an individual participant or all participants under this protocol
- Sexually active participants who refuse to use medically accepted barrier methods of contraception during the course of the study and for 3 months following last dose of study drug.
- Inability to tolerate a dose of 19.7mg freebase weight capsule (or 20mg tablet) (or saltweight equivalent which is 25mg tablet) of cabozantinib
- Cabozantinib treatment delays for greater than 6 consecutive weeks.
- Participant has missed > 2 consecutive planned doses of fulvestrant (applies to participants in fulvestrant/cabozantinib cohort only)
- Progressive disease as determined by the investigator.

The reason for study treatment discontinuation will be documented. For participants who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol-specified end of study visit unless consent to participate in the study is also withdrawn.

If a participant fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the participant cannot be reached by telephone, at the minimum a registered letter should be sent to the participant (or the participant's legal guardian) requesting contact with the clinic.

If a participant is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a participant withdraws consent to participate in the study, the reason for withdrawal will be documented and no study procedures or assessments will be performed and no further study data will be collected for this participant, other than the determination of survival status from public records such as government vital statistics or obituaries.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities for cabozantinib

Cabozantinib has been relatively well tolerated in participants with diverse malignancies that have been studied to date. The pattern of adverse effects has been consistent across studies and enrolled participant populations can often be managed by concomitant medications or cabozantinib dose reductions.

The general safety profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, PPE syndrome, skin rash, elevated liver function tests (including ALT and AST), thrombotic events (such as deep vein thrombosis [DVT] and PE), hypertension, asymptomatic increases of amylase and lipase as well as overt pancreatitis.

Anticipated AEs potentially related to the inhibition of VEGFR such as hypertension and proteinuria will be carefully monitored.

Management of diarrhea, rash, and PPE syndrome are presented in this section as these have been a common toxicity observed in this study.

Management of hypertension is presented in this protocol (and in Table 6.3) as guidelines have been modified from those presented in the IB (the threshold for dose reduction of cabozantinib

has changed from systolic blood pressure (BP) of 140 mmHg to systolic BP of 150 mmHg and from diastolic BP of 90 mmHg to diastolic BP of 100 mmHg).

This is based on continued clinical experience on open label cabozantinib studies indicating that the incidence of hypertension is relatively infrequent in participants treated with cabozantinib (21% overall with 4% Grade ≥ 3) and that hypertension is manageable.

6.2 Anticipated toxicities for fulvestrant

The most common, clinically significant adverse reactions occurring in ≥5% of patients receiving fulvestrant are: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Increased hepatic enzymes (ALT, AST, Alk Phos) occurred in >15% of faslodex patients and were not dose-dependent.

6.3 General guidelines for non-hematologic and hematologic adverse events

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Tables 6.1 and 6.2.

Table 6.1: Management of study treatment-related non-hematologic Toxicities

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

Dose modifications or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety. The Sponsor/Medical Monitor must then be informed.

Table 6.2: Management of Hematologic Toxicities

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

ANC, absolute neutrophil count.
Neutropenia: Grade 1 (LLN ≤ ANC < 1.5×10^9/L; Grade 2 (1×10^9/L ≤ ANC <1.5 x 10^9/L), Grade 3 (0.5×10^9/L ≤ ANC < 1×10^9/L), Grade 4 (ANC < 0.5×10^9/L).
Febrile Neutropenia CTCAE v4: Grade 3 (ANC<1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >= 38 degrees C (100.4 degrees F) for more than one hour.); Grade 4 (Life-threatening consequences; urgent intervention indicated)
Thrombocytopenia: Grade 1 (<LLN – 75 x 10^9/L);Grade 2 (<75.0 – 50.0 x 10^9/L) Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25 × 10^9/L).

6.4 Toxicity Management

6.4.1 Guidelines for Management of Treatment Emergent Diarrhea

Administration of antidiarrheal agents is recommended at the first sign of diarrhea. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate can be used. Additional agents to consider in participants with diarrhea that is refractory to the above include tincture of opium and octreotide. (46) Suggested guidelines for the management of cabozantinib-

induced diarrhea are outlined in Appendix F. Some participants may require concomitant therapy with loperamide, diphenoxylate, and tincture of opium to control diarrhea.

Evidence of steatorrhea associated with weight loss has been observed in two participants in the XL184-201 study, a Phase 2 study of single agent cabozantinib in participants with progressive or recurrent glioblastoma. These participants responded to therapy with pancrelipase. Possible workup for participants with diarrhea should include evaluation for steatorrhea.

Renal function and serum electrolytes should be monitored closely and corrected in participants with diarrhea or risk of dehydration.

6.4.2 Guidelines for Management of Treatment Emergent Rash Types

Palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported with cabozantinib. All participants on study should be advised on prophylactic skin care including the use of emollients, avoidance of exposure of hands and feet to hot water, 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. In general, aggressive management of symptoms is recommended for Grade 1 PPE syndrome. Aggressive management of symptoms is recommended, including early dermatology referral. Dose reduction of study treatment to the next lower dose at the first sign of hand-foot syndrome is strongly recommended.

Participants should be carefully monitored for signs of infection.

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

Hand-Foot Skin Reaction and Hand Food Syndrome (PPE)	
No apparent toxicity	Prophylaxis with Ammonium lactate 12% cream (Amlactin®) twice daily OR heavy moisturizer (e.g. Vaseline) twice daily
Grade 1	Continue treatment at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	Reduce study treatment to next lower level or interrupt dosing if not tolerated and monitor for changes in severity. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time (eg, peeling, blisters, bleeding, edema, or hyperkeratosis or affects self-care) or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If dosing was interrupted, treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

6.4.3 Guidelines for management of hepatobiliary disorders and elevations of amylase, lipase or pancreatitis

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

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

All subjects who develop bilirubin elevations ≥ 3 times the upper limit of normal should have study treatment held until recovered to Grade ≤ 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without

biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST or ALT less than or equal to the ULN at baseline	
Grade 1	Continue study treatment with biweekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue study treatment with at least weekly monitoring of LFTs for 2 weeks. Then biweekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumes at a one-dose-level reduction of XL184
Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumes at a one-dose-level reduction of XL184.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least weekly, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT > ULN – 2.5 x ULN at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade <3	Continue study treatment with at least twice weekly monitoring of LFTs for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumes at a one-dose-level reduction of XL184
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumes at a one-dose-level reduction of XL184.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least weekly, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a loweer dose as determined by the investigator and sponsor but only with sponsor approval.
Subjects AST or ALT > 2.5 – 5.0 x ULN at baseline	

≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumes at a one-dose-level reduction of XL184.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least weekly, until resolution to Grade ≤ 1. If the subject was clearly deriving clinical benefit, the subject may be able to resume treatment at a loweer dose as determined by the investigator and sponsor but only with sponsor approval.

Asymptomatic elevations of amylase, lipase as well as pancreatitis have been reported in subjects receiving cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but, in general, have not been associated with clinically apparent sequelae All subjects who develop lipase elevations of Grade ≥ 3 (> 2-5 times the upper limit of normal) should have study treatment interrupted. Amylase and lipase should be monitored at least 2 – 3 times per week. Cabozantinib may be restarted at the same dose or at a reduced dose after lipase levels have resolved to Grade ≤ 1 or baseline (or lower), provided that this occurs within 6 weeks. For asymptomatic pancreatitis with enzyme elevations >5 times the upper limit of normal (CTCAE Grade 4), restart study treatment at a reduced dose after lipase levels have resolved to Grade ≤ 1 or baseline (or better), provided that this occurs within 6 weeks.

If subjects have Grade ≤ 3 symptomatic acute pancreatitis (which may present with abdominal pain and/or nausea and/or fever) study drug should be interrupted. Study drug may be restarted at a reduced dose after lipase levels and pancreatitis resolve to Grade ≤ 1 or baseline (or lower), provided that this occurs within 6 weeks. If symptomatic pancreatitis recurs, study drug should be permanently discontinued. Subjects with Grade 4 pancreatitis should be permanently discontinued from study.

6.4.4 Guidelines for Management of Treatment Emergent Nausea/vomiting/mucositis/stomatitis

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting.

Agents classified as having a high therapeutic index (such as 5-HT3 receptor antagonists, or NK-1 receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or

dexamethasone are recommended (Hesketh et al. 2008, ASCO 2006; Roila et al, Annals of Oncology, 2010). Caution is recommended with the use of aprepitant or fosaprepitant and nabilone as cabozantinib exposure may be affected by concomitant administration because aprepitant and fosaprepitant are both inhibitors and inducers of CYP3A4, and nabilone is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Intervention to reduce the risk of stomatitis such as modification of ill fitting dentures and appropriate care of gingivitis should be instituted as indicated,

Stomatitis and mucositis should be managed with good oral hygiene and standard local treatments such as atraumatic cleansing and oral rinses (eg, with a weak solution of salt and baking soda). The oral cavity should be rinsed and wiped after meals, and dentures cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines.

6.4.5 Guidelines for management of embolism and thrombosis while patient is on study

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

Subjects who develop a PE and/or DVT should have study treatment interrupted until full anticoagulation is established with low molecular weight heparin (LMWH) (Full anticoagulation with warfarin is not permitted). Vena cava filters are not recommended due to the high incidence of complications associated with their use, except in subjects with a contra-indication to pharmacological anticoagulation. Once a subject is fully anticoagulated, treatment can be restarted at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects,

prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

6.4.6 Guidelines for management of treatment-emergent Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with other inhibitors of VEGF pathways. Proteinuria diagnosed by dipstick should be quantified by a urine protein/creatinine ratio (UPCR). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Details of management are described below:

Management of Treatment Emergent Proteinuria

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

6.4.7 **Rectal and Perirectal Abscess**

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

6.4.8 **Gastrointestinal perforation and GI fistula**

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

- Intra-abdominal tumor/metastases invading GI mucosa

- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing)

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

Additional risk factors include concurrent use of steroid treatment or non-steroidal anti-inflammatory drugs (Rodriguez et al. 2001, Straube et al. 2009). Constipation, consistent with symptoms of bowel obstruction, should be monitored and effectively managed. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

6.4.9 Guidelines for Management of Treatment Emergent Hypertension

Table 6.3 provides treatment guidelines for hypertension deemed related to cabozantinib. In general, participants with known hypertension should be optimally managed prior to study entry. Decisions to hold or decrease the dose of study treatment and to modify treatment of hypertension should be based on BP readings taken by a medical professional and must be confirmed by a second reading at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking new therapeutic action. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine.

Table 6.3: Guidelines for the Management of Treatment Emergent Hypertension

Criteria for Dose Modification	Study Treatment Dose Modification
Participants NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg OR	o Add new or additional antihypertensive medications and/or increase dose of existing medications. o Maintain dose of cabozantinib o If optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 systolic or < 100 diastolic, or if participant is symptomatic, dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	o Reduce cabozantinib by one dose level. o Add new or additional anti-hypertensive medications and/or increase dose of existing medications. o Monitor participant closely for hypotension. o Re-escalate cabozantinib at initial dose level if BP falls to < 150 systolic and < 100 diastolic mm Hg. o If optimal antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further.

BP, blood pressure.

6.4.10 Guidelines for Management of Treatment Emergent QTc prolongation:

Mild to moderate QTcF prolongation has been demonstrated in patients taking cabozantinib. Participants who have any additional risk factors for QTc prolongation, including those listed below, should have additional monitoring of EKGs while taking cabozantinib.

Factors to consider that may also contribute to prolongation in QTc:

- Treatment with other drugs associated with QTc prolongation including sotalol, quinidine, amiodarone, moxifloxacin, erythromycin and azithormycin. (For comprehensive lists please see http://www.qtdrugs. org)
- Treatment with CyP3A4 inhibitors (which may increase cabozaninib drug levels)

- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia)
- Medical conditions which can alter electrolyte status (e.g., severe or prolonged diarrhea)
- **Cabozantinib should be taken in a fasted state.** Cabozantinib exposure (AUC) increases about 57% when it is taken with food. Confirm with participants that the drug is being taken in a fasted state.

If at any time a participant is receiving cabozantinib and there is an increase in QTc interval to an absolute value >500 msec, two additional EKGs should be performed within 30 minutes after the initial EKG with intervals no less than 3 minutes apart. If the change is noticed and the subject is not in the clinic, the subject should be notified immediately and brought to a medical facility to be evaluated as soon as possible with additional EKGs. If the average QTcF from three EKGs is >500 msec, study treatment with cabozantinib must be withheld and the following actions should be taken:

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

Exelixis should be notified immediately of any QTc prolongation event. Participants with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic participants must be treated according to standard clinical practice. No additional cabozantinib is to be given to the participant until after the event has resolved and the participant has been thoroughly evaluated. If any additional study treatment is given (e.g. after correction of electrolyte abnormalities and normalization of QTcF), it should be at a reduced dose as determined by the investigator.

6.5 Dose Modifications/Delays

Participants will be monitored continuously for AEs through 30 days (+7 days) after the last dose of study treatment. Participants will be instructed to notify their physician immediately for any and all toxicities. Participants experiencing one or more AEs due to the study treatment may require

a dosing delay, or reduction(s), in their dose in order to continue with study treatment. Assessment of causality (chronology, confounding factors such as disease, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be documented by the PI when possible, before a decision is made to modify the dose or to hold dosing temporarily.

The criteria presented in this section for dose modifications and delays are meant as general guidelines:

As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Should this be ineffective, a dose delay or dose reduction may be considered to avoid worsening toxicity. Please refer to Table 6.4 for the dose reduction levels for study treatment. (Table A1.2 located in Appendix A provides equivalent dosing information for patients treated with tablet formulation)

If a participant develops unacceptable toxicity as defined below that is determined to be at least possibly related to study treatment, and if supportive care measures and/or a dose reduction fails to lessen the toxicity to acceptable levels, study treatment should be withheld.

Unacceptable toxicity:

- Intolerable Grade 2 toxicity (except alopecia) that cannot be adequately managed with supportive care and/or a dose reduction
- Intolerable rash of any grade that cannot be adequately managed with supportive care and/or a dose reduction
- Any Grade 3 or Grade 4 toxicity despite optimal management that poses a significant clinical risk (including nausea, vomiting, diarrhea, hypertension)
- Urine protein/ creatinine ratio > 2
- Grade 4 thrombocytopenia or anemia
- Grade 4 neutropenia > 5 days duration
- Grade ≥ 3 neutropenia of any duration with fever (> 38.5°C) or documented infection

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

1. All treatment interruption and dose reductions should be communicated to the Principal Investigator by entering into Electronic case report forms within 72 hours.
2. If study drug is withheld for a treatment-related toxicity, re-initiation of study treatment cannot occur until toxicity decreases to ≤ Grade 1 or baseline value (or lower).
3. The minimum dose of study treatment will be 19.7mg freebase capsule (or 20 mg tablet or salt weight equivalent) PO qd. Participants who cannot tolerate this dose, or for whom

treatment-related toxicity does not resolve to Grade ≤ 1 or baseline within 6 weeks after a dose interruption, will have the relevant study drug discontinued.

4. If the participant recovers from his or her toxicities (per the criteria above) to Grade ≤ 1 or to the baseline value (or lower) within 6 weeks and the toxicity was deemed related or possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 6.4) Participants receiving the lowest dose of study treatment may be restarted at the same dose at the discretion of the investigator. If the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.
5. Participants who develop a PE and/or deep vein thrombosis (DVT) should have study treatment held until therapeutic anticoagulation is established. Once a subject is fully anticoagulated with LMWH, treatment can be restarted at one dose lower. Guidelines for anticoagulation thereafter are outlined in section 6.3.5
6. Participants may be re-escalated to the previous dose at the discretion of the investigator no sooner than 2 weeks beyond resolution (Grade ≤ 1 or to the baseline value [or lower]) of AEs.
7. Participants will enter the Post-Treatment Period after the last administration of study treatment.
8. Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with sponsor approval. The acceptable length of interruption will depend on agreement between the investigator and the sponsor.
9. If study treatment is interrupted, the participant should be instructed not to make up the withheld doses, and the planned safety and tumor assessment schedule are to be maintained.

Table 6.4: Dose Reductions of Study Treatment for patients treated with cabozantinib 20mg tablets[a]

Starting Dose[b]	**First Level dose Reduction**
40mg cabozantinib	Reduce to 20mg cabozantinib

[a] Participants may be re-escalated to the previous dose at the discretion of the investigator no sooner than 2 weeks beyond resolution (Grade ≤ 1 or to the baseline value [or lower] of AEs).
[b] Dosing refers to free base weight throughout
[c] Participants who cannot tolerate study treatment at 19.7 mg capsules (or 20 mg tablets or salt weight equivalent) PO will be discontinued from study treatment.

6.6 Dose reductions for Endocrine combination cohort

Dose-reductions for cabozantinib will be the same as described above for patients in the endocrine combination cohort. There will be no routine dose-reductions for fulvestrant, however a 250 mg dose of fulvestrant is recommended in patients with moderate hepatic impairment.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Cabozantinib

Cabozantinib will either be supplied as 20mg freebase tablets. . For a description of the salt and freebase equivalent weights of doses and capsule strengths mentioned in this study, see **Appendix A**. The cabozantinib tablet components are available in **Appendix A**.

7.1.1 Description

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

7.1.2 Storage

Cabozantinib must be stored at room temperature

7.1.3 Compatibility

Not applicable

7.1.4 Handling

Not applicable

7.1.5 Availability

Cabozantinib is an investigational agent and will be supplied free-of-charge from Exelixis.

7.1.6 Preparation

Not applicable

7.1.7 Administration

Cabozantinib is administered once daily as an oral tablet. Participants will be provided with a sufficient supply of study treatment and instructions for taking the study

treatment on days without scheduled clinic visits. After fasting (with exception of water) for 2 hours, participants will take study treatment daily each morning with a full glass of water (minimum of 8 oz/ 240 mL) and continue to fast for 1 hour after each dose of study treatment. If doses are withheld, the original schedule of assessments should be maintained when cabozantinib is restarted. The participant should be instructed to not make up the missed doses and to maintain the planned dosing schedule. Participants must be instructed to not make up missed doses that are vomited.

7.1.8 Ordering

Cabozantinib will be provided by Exelixis.

7.1.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of cabozantinib using the NCI Drug Accountability Record or another comparable drug accountability form.

7.1.10 Destruction and Return

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

7.2 Drug Information for Pilot Fulvestrant/Cabozantinib Combination Cohort

Fulvestrant will each be administered as per standard prescribing information. The cost of these medicines will be charged as standard of care to the patient/patient's insurance company.

7.2.1 Pharmacology for Fulvestrant/Cabozantinib Combination Cohort

Cabozantinib:
Cabozantinib is a substrate for CYP3A4 metabolism in vitro, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 *N*-oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on XL184 metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction). Administration of strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance and increased single-dose plasma cabozantinib exposure (AUC range: 34-38% higher). In contrast, administration of strong CYP3A4 inducer rifampin (600 mg

daily for 31 days) to healthy volunteers increased cabozantinib clearance and decreased single-dose plasma cabozantinib exposure (AUC range: 76-77% lower). Coadministration of strong CYP3A4 inhibitors with cabozantinib should be approached with caution; chronic coadministration of strong CYP3A4 inducers with cabozantinib should be avoided.

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (apparent inhibition constant, Ki_{app} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Ki_{app} = 10.4 μM) and CYP2C19 (Ki_{app} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Ki_{app} = 282 μM) in HLM preparations. IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib at clinically-relevant steady-state plasma concentrations (≥125 mg/day daily for a minimum of 21 days) showed no statistically-significant effect on single-dose plasma PK exposure values (C_{max} and AUC) for CYP2C8 substrate rosiglitazone in subjects with solid tumors. Thus, cabozantinib appears to present low potential for inhibiting metabolism of concomitant medications at clinically-relevant exposures that are substrates for CYP2C8 and other CYP isozymes demonstrating less potent inhibition by XL184 in vitro.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities. As few drugs are metabolized through the CYP1A1 pathway, the limited CYP induction potential of cabozantinib does not appear to be clinically-significant.

Cabozantinib is an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Cabozantinib appears to be a more potent P-gp inhibitor (IC_{50} = 0.5 ± 0.2 μM) in a Caco-2 cell monolayer assay system. Subjects should be cautioned regarding taking a P-gp substrate while receiving cabozantinib.

Fulvestrant:
As per Chouinard, et.al Mol Pharmacol 2006, fulvestrant is glucuronidated by UGT1A1, 1A3, 1A4 and 1A8. There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers.
(Fulvestrant prescribing information, most recent update Sept 2010)
Hepatic Impairment: A 250 mg dose is recommended in patients with moderate hepatic impairment.

See Appendix I for table of CYP450 Clinically Significant Drug Interaction Table

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies (applicable only to first 14 patients in fulvestrant/Cabozantinib Combination Cohort)

Pharmacokinetic samples will be obtained to assess whether or not the plasma pharmacokinetics of cabozantinib are altered by the concurrent administration of fulvestrant. Pharmacokinetic sampling will be performed on days 15-16 of cycle 1, after steady-state pharmacokinetic conditions for the once daily dosing schedule have been achieved, to define the cabozantinib plasma concentration-time profile over a single 24 h dosing interval. The apparent oral clearance of the drug will be estimated from the area under the plasma concentration-time curve for the 24 h dosing interval. The potential effect of fulvestrant on the pharmacokinetics of cabozantinib will be determined by comparing the mean apparent oral clearance of the drug for patients participating in this clinical trial to data from previous single agent studies.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients are to be instructed to take the doses of cabozantinib at the same time every day during cycle 1. Cabozantinib should be taken at a time that will allow the patient to arrive at the clinic to obtain a pharmacokinetic sample before dosing and to remain for an additional 8 hours. The day 15 dose of fulvestrant may be administered at any time during the day 15 visit. The actual sampling schedule and procedures that are to be used to establish times, collect samples, and process specimens for storage and shipment prior to analysis are described in Appendix J.

The concentration of carbozantinib will be determined separately by validated analytical methods based upon reversed-phase high-performance liquid chromatography with electrospray ionization mass spectrometry. Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional Version 4.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Mean values of pharmacokinetic parameters will be statistically compared using the two-tailed t-test of the log-transformed data.

8.2 Pharmacodynamic Studies

8.2.1 Laboratory Correlative Studies

8.2.2 Bone Turnover Markers

8.2.2.1 The Clinical Laboratory Research Core (CLRc) will receive specimens from Massachusetts General Hospital and accession them under unique laboratory barcode identifiers. The testing and services will be conducted in a CLIA approved facility. The laboratory will outsource testing for some bone marker tests to LabCorp. Following receipt of specimens, the laboratory will be responsible for all specimen tracking, testing and reporting. Serum concentrations of C-telopeptide, bone alkaline phosphatase, osteocalcin and serum N-telopeptide

will be measured by enzyme immunoassays. Serum Procollagen type 1 N-terminal peptide will also be measured. Urinary N-telopeptide will be measured by enzyme immunoassays. Samples will be collected prior to start of therapy and on Day 1 of each cycle (every 3 weeks) through to Off study Visit.

8.2.2.2 External participating sites will ship serum and urine samples to the CLRc on dry ice according to IATA guidelines (UN3373 Label) by Federal Express for next-day delivery to:

Clinical Laboratory Research Core

Bulfinch Bldg., Suite 051

Massachusetts General Hospital

70 Blossom Street

Boston, MA 02114

Phone: (617) 726-3364

Samples must be accompanied by a requisition identifying the study number, DF/HCC protocol 11-208.

8.2.3 Tumor Markers

Blood samples will be collected for tumor marker analysis according to the study calendar in section 9.1. CA27-29 or CA15-3 will be analyzed depending on which is standard at the participating site. All tumor marker assessments will be performed at the local laboratory.

8.2.4 Circulating Tumor Cells

For participants in the cabozantinib/fulvestrant cohort, blood samples for circulating tumor cell enumeration will be collected at baseline and at each cycle.

Briefly, 7.5 mls of whole blood (1 tube) will be collected in CellSave^{R} preservative tubes. Samples can sit at room temperature for up to 96 hours but must be inverted immediately to help prevent clotting. CTC samples from participants being treated at the DF/HCC hospitals will be processed by the CLIA-certified CTC Laboratory at Brigham and Women's Hospital using the validated FDA-approved CellSearch^{R} System (Veridex) for enumeration. The sample is first enriched for CTC using immunomagnetic beads conjugated with anti-EpCAM antibodies. The captured cells are permeabilized and labeled with cytokeratin and CD45 specific antibodies and the nuclear stain '4-6 Diamidino-2-phenylindole (DAPI). Stained cells are collected by the Veridex system in a "MagNest" cartridge. This cartridge is automatically scanned and CTC manually counted according to the manufacturer's instructions by a trained pathologist. CTC samples from participants being treated at MSKCC will be assayed by the same techniques performed at the MSKCC Clinical Chemistry Research laboratory. For sample collection and processing

instructions, please see Appendix K. Samples will be collected and processed the same way at Memorial Sloan Kettering Cancer Center.

8.2.4 Pain Questionnaire and Analgesic Medication Diary

For the purpose of determining the effect of cabozantinib treatment on pain and analgesic medication usage, pain will be assessed by a participant-reported questionnaire, and daily analgesic medication usage will be recorded during regular intervals. All participants are required to complete assessments, regardless of whether pain is present or analgesic medications are being taken at baseline.

Pain assessments will consist of patient-reported responses to a questionnaire (see Appendix E), administered by paper, in which participants will be asked to rate their pain and degree of interference in daily activities due to pain over the prior 24 hours. (Items from the MD Anderson Symptom assessment inventory;(47)), as well as their pain relative to their prior assessment (adapted from the Subjective Significance Question; (48)). The participant will complete this pain questionnaire each day for a 7-day interval within 14 days of the first dose of study treatment and at 7-day intervals during Cycle 3, Cycle 6, and every 6 weeks thereafter until the date of the participant's last extended follow-up visit or last scan, whichever is longer, according to the schedule in section 9.1.

Analgesic medications will be recorded on a daily participant diary matching the dates of the pain questionnaire (described above).Analgesic medications to be recorded on the diary include narcotics and corticosteroids used to treat pain symptoms. Every effort should be made to collect responses for every day during the 7 day assessment interval. However, collection of a minimum of 4 out of the 7 days in the interval (need not be consecutive) will be deemed sufficient for assessment completion.

For participants in the Fulvestrant/Cabozantinib combination

Pain questionnaire and medication diary is to be completed each day for a 7-day interval within 14 days of the first dose of study treatment and during the first 7 days (+/- 3 days) of Cycle 2, Cycle 4, and every 8 weeks thereafter until the date of the participant's last extended follow-up visit or last scan, whichever is longer, according to the schedule in section 9.1.

9. STUDY CALENDAR

Table 9.1 Schedule of Assessments for main study participants Each cycle is 21 days

	Pretreatment							
Assessments/ Procedures	**Screening[A] (≤ 28 days)**	**Cycle 1 Day 1**	**Cycle 2 Day 1 (± 4 days)**	**Cycle 3 Day 1 (± 4days)**	**Cycle 4 Day 1 (± 4 days)**	**Cycle 5 Day 1 (±4 days)**	**Cycle 6 Day 1 and Subsequent Cycles Day 1 (±4 days)**	**End of Study[H]**
Informed consent	X							
Demographics	X							
Medical and cancer history	X			X		X	X	X
Physical examination[C]	X	X[B]	X	X	X	X	X	X
Vital signs[D]	X	X[B]	X	X	X	X	X	X
EKG [N]	X		X					
ECOG performance status	X	X[B]	X	X	X	X	X	X
CBC w/ diff	X	X[B]	X	X	X	X	X	X
PT/INR or PTT	X	X[B]	X	X	X	X	X	X
Serum chemistry[E]	X	X[B]	X	X	X	X	X	X
UA including urine protein	X	X[B]		X		X	X	X
TSH	X	X[B]		X		X	X	X
Serum/urine pregnancy test[F]	X	X[B]	X		X		X Every 12 weeks	
CA 27.29 or CA15.3	X	X[B]	X	X	X	X	X	X
Serum amylase and lipase	X	X[B]	X	X	X	X	X	X
Serum/Urine for bone turnover markers[G]		X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events[H]	X	X	X	X	X	X	X	X
Dispense drug		X	X	X	X	X	X	
Drug diary		X	X	X	X	X	X	
Bone scan [I]	X					X	Every 12 weeks [J]	X
FDG PET/CT with contrast [I]	X					X	Every 12 weeks [J]	X
Survival follow-up								X[k]
7-day pain questionnaire[L]	X			X			Every 6 weeks [m]	
7-day analgesic medication diary [L]	X			X			Every 6 weeks [L]	

[A] Screening assessments must occur within 28 days before initial dose of study treatment. Informed consent must be provided before any study-specific procedures are performed and within 28 days of registration.

[B] If performed <7 days before the first dose of study treatment, these screening procedures do not need to be repeated on Cycle 1 Day 1. If these procedures are performed on Cycle 1 Day 1, then the results must be available and reviewed by the treating physician prior to administering study treatment.

[C] Complete physical examination with height and weight (Height only required at screening)

[D] Includes blood pressure, pulse, respiratory rate, temperature

[E] Complete Serum chemistry panel includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, phosphorus, sodium, total bilirubin, total protein.

[F] For women of child bearing potential

[G] For serum and urine for bone turnover markers assessments, one 10 ml red top and one spot sterile urine sample should be collected and sent to the MGH CLR for processing. . Label with initials, assigned participant number, study number, date, and body fluid type (serum or urine).

[H] Adverse events information will be collected at study visits and may, in addition, be collected over the phone. Adverse events that occur after Informed Consent and prior to the first dose of study drug should be recorded in the appropriate Medical History (General) CRF. A separate end of study visit is not required if patients are examined and have data collected at time of 'off study' visit. If patients are not seen when they come of study, every attempt should be made to have an End of Study Visit completed within 30 days (+/- 7 days) of last dose of study drug.

[I] Screening PET/CT and bone scan must be completed within 28 days of initial dose of study treatment. All other scans should be completed within 7 days of the protocol timepoint. Patient should remain on current dose until results are available from central review. If bone biopsy is being performed, it should be collected AFTER the radiologic assessments.

[J] Completed every 12 weeks after Cycle 6 Day 1.

[K] Survival follow-up annually for five years or death

[L] The participant will complete the pain questionnaire and medication diary each day for a 7-day interval within 14 days of the first dose of study treatment and at 7-day intervals during Cycle 3, Cycle 6, and every 6 weeks thereafter. Analgesic medications to be recorded on the diary include narcotics and corticosteroids used to treat pain symptoms.

[N] Participants who have known risk factors for QTc prolongation should have additional monitoring EKGs. Please refer to section 6.4.10 for a list of risk factors and guidelines for management.

O: Nursing assessment of toxicity; contact MD with any new toxicities and evaluate management with MD/PI.

Table 9.1 Schedule of Assessments for patients on Fulvestrant/Cabozantinib Combination cohort.

Each treatment cycle is 28 days.

[A] Screening assessments must occur within 28 days before initial dose of study treatment. Informed consent must be provided before any study-specific procedures are performed and within 28 days of registration.

[B] If performed <7 days before the first dose of study treatment, these screening procedures do not need to be repeated on Cycle 1 Day 1. If these procedures are performed on Cycle 1 Day 1, then the results must be available and reviewed by the treating physician prior to

Assessments/procedures	Screening ≤days [A]	Cycle 1 Day 1 **(± 4 days)**	Cycle 1 Day 15 [H]	Cycle 1 day 16 [H]	Cycles 2 and 3 Day 1 **(± 4 days)**	Cycle2 and 3 Day 15 **(± 4 days)**	Cycle 4 Day 1 and subsequent cycles **(± 4 days)**	End of Study[G,K]
Informed Consent, Demographics, Medical and Cancer history	X							
Physical Examination[C]	X	X[B]	X[N]		X		X	X
Vital signs[D]	X	X[B]	X		X		X	X
EKG[E]	X				X		Every 12 weeks	
ECOG performance status	X	X[B]	X		X		X	X
CBC w/diff	X	X[B]			X		X	X
PT/INR or PTT	X	X[B]	X		X		X	X
Serum chemistry[F]	X	X[B]	X		X	X	X	X
UA including urine protein	X	X[B]	X		X		X	X
TSH	X	X[B]			X		X	X
CA27.29 or CA15.3 and CTCs		X[B]			X		X	X
Serum amylase and lipase	X	X[B]	X		X	X	X	X
Concomitant medications	X	X			X		X	X
Adverse events[G]	X	X	X		X		X	X
PK samples			X[H]	X[H]				
Dispense Cabozantinib		X			X		X	
Dispense fulvestrant		X	X		X		X	
Drug diary		X			X		X	
Bone scan [I]	X						Every 12 weeks [J]	X[K]
CT with contrast[I]	X						Every 12 weeks [J]	X[K]
Survival follow-up								X[L]
7-day pain questionnaire [M]	X				X		Every 8 weeks [M]	
7day analgesic medication diary [M]	X				X		Every 8 weeks [M]	

administering study treatment. CA27.29 or CA15.3 and CTCs may be collected on Cycle 1, Day 1 or <7 days before first dose of study treatment.

[C] Complete physical examination with height and weight

[D] Includes blood pressure, pulse, respiratory rate, temperature

[E] Participants who have known risk factors for QTc prolongation should have additional monitoring EKGs. Please refer to section 6.4.10 for a list of risk factors and guidelines for management

[F] Complete Serum chemistry panel includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, phosphorus, magnesium, sodium, total bilirubin, total protein.

[G] Adverse events information will be collected at study visits and may, in addition, be collected over the phone. Adverse events that occur after Informed Consent and prior to the first dose of study drug should be recorded in the appropriate Medical History (General) CRF. A separate end of study visit is not required if patients are examined and have data collected at time of 'off study' visit. If patients are not seen when they come of study, every attempt should be made to have an End of Study Visit completed within 30 days (+/- 7 days) of last dose of study drug.

[H] PK samples required for first 14 patients only. Blood samples (6 mL) will be obtained shortly before taking the day 15 dose of cabozantinib and at 0.5h(± 15 min), 1.0h(± 15 min), 2.0h(± 15 min), 3.0h(± 15 min), 4.0h(± 30 min), 6.0h(± 30 min), 8.0h(± 30 min), and 24.0 h(± 1 h)(ie day 16) after dosing. It is very important that the patient is aware that the morning dose of cabozantinib on day 16 must not be taken before arriving at the clinic and the 24.0 h pharmacokinetic sample has been collected.

[I] Screening CT and bone scan must be completed within 28 days of initial dose of study treatment. All other scans should be completed within 7 days of the protocol timepoint. Patient should remain on current dose until results are available from central review.

[J] Completed at Cycle 4 day 1 and every 12 weeks thereafter

[K] Bone scan and CT to be repeated at 30-day visit +/- 7 days ONLY if patient came off study for reasons other than documented progression of disease.

[L] Survival follow-up annually for five years or death

[M] The participant will complete the pain questionnaire and medication diary each day for a 7-day interval within 14 days of the first dose of study treatment and during the first 7 days (+/- 3 days) of Cycle 2, Cycle 4, and every 8 weeks thereafter. Analgesic medications to be recorded on the diary include narcotics and corticosteroids used to treat pain symptoms.

[N] Limited assessment by research nurse for adverse event review

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect

All participants in the main study are to be assessed using Technetium-99 MDP Bone Scan, and whole body PET scans and diagnostic CT scans of the chest, abdomen, and pelvis with iodinated IV contrast as shown in table Table 9.1, Schedule of Assessments. Please note the PET scans and diagnostic CT scans may be performed on the same scanner, one immediately following the other, or on different systems on the same day, as long as each scan type is obtained on the same make and model equipment for a given patient across time points. Patients in the pilot fulvestrant/cabozantinib cohort will be followed by bone scan and CT only. Tumor assessments will be performed at screening, and approximately every 12 weeks thereafter following the first dose of study treatment. Assessments will continue until the earlier of documented PD or the initiation of subsequent anticancer therapy. Assessments should continue even if study treatment is being held or discontinued for reasons other than PD. For this study the primary study endpoint is percentage response rate in bone metastases as assessed on bone scan from baseline. Bone scans will be centrally reviewed.

10.1.1 Image Acquisition Parameters

Imaging acquisition parameters should follow local standard of care when possible, within the constraints detailed throughout this section. A diagnostic CT should include full coverage of chest, abdomen, and pelvis at all specified time points in Table 9.1. This should include a standard post intravenous iodinated contrast phase. A pre- contrast scan is not required. CT acquisition collimation should be less than or equal to 3 mm, and reconstructed axial images should be provided at 5mm or less slice thickness in a soft tissue kernel. The reconstructed series must be submitted. A diagnostic CT scan performed immediately after the PET scan on the same combined multichannel PET-CT scanner is preferred. At sites where this is not possible, the diagnostic CT scan should be performed on a dedicated multichannel CT within the same week as the dedicated PET scan. Please note, the diagnostic CT scan is in addition to any non-diagnostic low maS-dose attenuation correction CT scan that may be performed as part of the PET reconstruction.

Whole body, anterior and posterior bone scans should be acquired using 20-25 mCi Tc-99m Methylene diphosphonate (MDP) administered intravenously with imaging performed at 3 hours +/- 30 min post injection. At all scheduled follow up bone scans the same dose of technetium and same 3 hr +/- 30 min delay from injection to scanning must be used, both of which should be

documented on the appropriate CRF. For participants with symptoms of spinal compression, MRI of the spine and base of the skull should be performed.

The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response. (49) Patients should avoid strenuous exercise for 24 hours prior to the scan. Patients should fast for 6 hours or longer prior to the FDG injection and should have a serum glucose of less than 225 mg/dL at the time of FDG injection. A 15-25 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan.

NOTE: It is very important that the same method of radiological assessment be used throughout the study. In particular all participants should be scanned using the same modality and imaging protocol as used at baseline at all subsequent imaging time points.

10.1.2 Central Independent Radiology Facility (IRF)

An IRF will evaluate bone scans, whole body FDG-PET/CTs and supportive clinical data of trial participants in a central and independent fashion. The IRF will be comprised of board-certified radiologists who will determine response and/or progression. Details regarding IRF member qualification, training, methods, procedures, and other issues relevant to IRF will be described in the IRF charter.

The IRF will not perform independent clinical evaluations. During radiographic evaluation, the IRF will consider clinical factors that impact the interpretation of bone scans (see Section 10.1.3).

Bone and FDG PET/CT scans done at screening and 12 week intervals must be sent to the IRF as detailed below. All bone scans sent to the IRF must be in original Digital Imaging and Communications in Medicine (DICOM) format. Electronic transfer of scan files (via FTP, HTTP, or similar means) is preferred, though transfer on physical media (such as DVDs or CDs) is acceptable. For digital media, one time point per-participant-per-disk is expected.

10.1.3 Bone Scan Response Assessment per Independent Review Facility (IRF)

Initially the bone scan will be categorized according to well-defined published criteria: normal/benign: absence of uptake or focal increased uptake typical for a benign origin (eg, fracture, degenerative joint disease, Paget's disease of bone, and so on); positive for bone metastases: presence of either (multi)focal or diffuse (superscan) uptake typical for metastatic disease; and equivocal: image could not be confidently categorized as one of the former two

subgroups, hence requiring additional imaging procedures. At each timepoint, the positive area on a bone scan (PABS) will be computed using semi-automated CAD software which segments each lesion based on image intensity and then sums the individual areas of lesion(s) to give an overall measure of bone tumor burden. Response is then determined based on the percent change from baseline in the Bone Scan Area (%BSA) as detailed in the IRC Charter.

10.1.4 Clinical Factors Affecting Tumor Assessment

Clinical information for the purpose of identifying and accounting for factors that may influence the interpretation of bone scans will be documented in the source materials and case report forms at the time of the screening and 12 weekly tumor assessments. Information to be collected includes:

- Radiotherapy during study treatment
- Fracture/trauma during study treatment
- Infection during study treatment
- Cytology during study treatment
- Local intervention during study treatment eg. Resection, biopsies

10.1.5 Definitions

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

Evaluable for response. Only those participants who have received at least 6 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle will also be considered evaluable.) Participants who do not meet the criteria for being evaluable for response defined above may be replaced to reach the sample sizes per section 14.

10.1.6 Response Criteria

Evaluation of Bone Lesions on bone scan

- Complete Resolution
- Significant Improvement
- Stable Disease
- Unequivocal Progression

Evaluation of Best Overall Response: The best overall response is the best response recorded from the start of the treatment. Criteria for investigator evaluation of response and determining treatment discontinuation due to

progressive disease are defined in Table 10.1. For evaluation of bone scan response per IRF, see Section 10.1.3.

mRECIST 1.1 criteria and criteria for bone scan assessment are detailed in Appendices B and C.

Table 10.1:Tumor Evaluation and Criteria for Treatment Discontinuation due to Progressive Disease for Investigators

CT/PET-CT Soft Tissue Assessment[a]	Bone Scan Assessment[b]	Progressive Disease Criteria for Treatment Discontinuation
mRECIST 1.1 (Appendix B)	Appendix C	PD of soft tissue lesion(s) per mRECIST 1.1; or Unequivocal worsening of bone scans

[a] Applied to patients with measurable soft-tissue lesions and may include soft-tissue component of bone lesions.

[b] For patients with metastatic lesions in bone only, Technetium-99 MDP.

Changes in tumor markers will not be considered for determination of PD.

Although study treatment may be discontinued by the investigator based upon clinical deterioration, every effort should be made to document PD using radiographic methods. The basis for discontinuation of study treatment due to clinical deterioration should be documente

10.1.7 Progression Free Survival (PFS) is defined as the time from randomization until the earlier of the following events: documented radiographic progressive disease or death due to any cause.
Response Review

All radiology assessments will be sent for central review with simultaneous review of the participants' files.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Suspected adverse reaction

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.

11.1.3 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events <u>not</u> considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen

- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.4 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

For the purposes of this study, a related adverse event (suspected adverse reaction) is considered 'unexpected' if it is not listed in the Investigator's Brochure or it is not listed at the specificity or severity that has been observed.

11.1.5 Attribution

Attribution is the causal relationship between the adverse event or serious adverse event and the study treatment. Causality assessment by the investigator will be based on the following two definitions:

- Not Related: A not related AE is an AE that is not associated with study treatment and is attributable to another cause.

- Related: A related AE or suspected adverse reaction is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable possibility is meant to convey that there are facts (e.g. evidence such as de-challenge/re-challenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.3.1 Serious Adverse Event Reporting

All serious adverse events that occur after informed consent, during treatment, or within 30 days of the last dose of study treatment must be reported to the DF/HCC Overall Principal Investigator and to Exelixis on Medwatch 3500A form. Serious adverse events occurring after the 30-day follow-up visit that are assessed as related to study treatment must also be reported to the DF/HCC Overall Principal Investigator and to Exelixis on Medwatch 3500A form. This includes events meeting the criteria outlined in Section 11.1.3.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator and to Exelixis within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event.

Report serious adverse events by email or facsimile to DF/HCC Overall Principal Investigator and to Exelixis Drug Safety:

Steven Isakoff, MD, PhD Telephone# (617) 726-4920
email: SIsakoff@mgh.harvard.edu
Fax# (617) 643-0589

And

Exelixis Drug Safety
Email: drugsafety@exelixis.com
Fax: 650-837-7392

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.3.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.4 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS) and send a copy of the submitted report to the DF/HCC Overall Principal Investigator. External participating sites will also report all serious adverse events to their local IRB using their local forms.

11.5 Reporting to the Food and Drug Administration (FDA)

As soon as an investigator becomes aware of an adverse event that meets the definition of 'serious,' this should be documented to the extent that information is available.

This report must be submitted by the study site to Exelixis or designee within 24 business hours, even if it is not felt to be drug related.

Email: drugsafety@exelixis.com; Fax 650-837-7392

The DF/HCC PI and staff will submit all IND Safety Reports in the form of MedWatch 3500A forms to Exelixis and the FDA. External participating sites must submit completed Medwatch 3500A forms to the DF/HCC PI, Steven Isakoff, MD, PhD (SIsakoff@mgh.harvard.edu) and study coordinator, Lauren Kaplan (lrkaplan@mgh.harvard.edu).

The investigator agrees to provide supplementary information requested by the Exelixis Drug Safety personnel or designee.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

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

These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form). The final MedWatch must be submitted by the study site to Exelixis on the same day it is submitted to the FDA to allow Exelixis time to cross-report to Exelixis' IND.

Email: drugsafety@exelixis.com; Fax 650-837-7392

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

11.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

11.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator, their respective IRB and Exelixis Drug Safety of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Data Submission

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

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

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

12.2 Safety Meetings

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

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

12.3 Monitoring

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

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

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

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

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

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

13.2 Informed Consent

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

13.3 Ethics and Good Clinical Practice (GCP)

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

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

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

13.4 Study Documentation

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

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

13.5 Records Retention

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

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix G).

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

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

14. STATISTICAL CONSIDERATIONS

This is an open-label, single arm study of cabozantinib, a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGFR2, RET, and KIT, in patients with hormone-receptor-positive metastatic breast cancer with involvement of bone. Up to fifty (50) evaluable patients will be treated with Cabozantinib 100mg freebase weight daily (or lower starting doses of 60mg or 40mg freebase weight where applicable). The primary endpoint is the bone scan response rate. The study will undergo one interim monitoring for futility when 17 evaluable patients have been accrued, dosed, and followed until the 12 week disease evaluation.

14.1 Study Design/Endpoints

The primary endpoint of this study is bone scan response rate defined as percentage of patients experiencing a complete resolution of bone scan lesions or significant improvement in bone scan lesions. As patients with bone-only disease have traditionally been excluded from clinical trials in breast cancer, we do not have historical response rates on which to base our assumptions. However, overall response rates for the 2nd line treatment of metastatic breast cancer in clinical trials of hormonal agents in hormone-receptor-positive breast cancer are usually less than 10%. (17)

This study will enroll a total of 50 evaluable patients in two stages (Simon design using PASS software), with 92% power to detect a response rate in bone of 30%, compared to a null response rate of 10%. 17 evaluable patients will be enrolled in the first stage and 33 evaluable patients will be enrolled in the second stage, for a total enrollment of 50 evaluable patients. After the first stage of accrual is complete, the study will suspend while patients are evaluated for bone response. If 2 or fewer patients achieve a bone response, the study will be terminated. If 3 or more patients achieve a bone response, the trial will continue to the second stage of accrual. If the true response rate is actually 10%, there is a 76% probability associated with terminating the study after the first stage of accrual. If the second stage of accrual is completed and the total number of responses on the study is 7 or fewer, cabozantinib will not be considered promising for future studies. If there are at least 8 bone responses on study, this will

provide evidence that cabozantinib warrants further study. If cabozantinib truly is not effective, there is only an 8% probability of concluding that it is based on this trial design.

14.2 Sample Size/Accrual Rate

The planned total sample size is 50 evaluable patients and the anticipated accrual is 2 participants per month at each study site (DF/HCC and MSKCC), for a total of 4 participants per month. Allowing for delay while first stage participants are analyzed, completion of accrual is thus expected to occur within 16 months.

A further 20 patients will be accrued to a combination fulvestrant/cabozantinib cohort. Inclusion criteria for this cohort are slightly stricter; therefore estimated accrual is 2-3 patients/month from all sites combined. There will be a delay while the first 14 patients are analyzed, thus completion of this cohort is expected to occur within 18 months of opening of this cohort.

14.3 Stratification Factors

No stratification factors will be used in the primary analysis, bone response rate.

Secondary survival analyses, including progression-free survival (PFS) and overall survival (OS) will be stratified by bone lesions only vs. bone and soft-tissue lesions. Additional details of these analyses are discussed in section 14.4.

14.4 Analysis of Secondary Endpoints

Secondary endpoints of this trial include:

- Overall response rate (ORR) (defined as the percentage of patients experiencing a complete response or a partial response)
- Overall Survival (OS)
- Progression-Free Survival (PFS)
- Effects of cabozantinib on biochemical markers of bone turnover and tumor markers
- skeletal related event rates in study participants
- FDG-PET/CT response rate

For Pilot Combination Fulvestrant/Cabozantinib Cohort

- To evaluate the safety and tolerability of concomitant administration of cabozantinib and fulvestrant in postmenopausal female patients with locally advanced or metastatic hormone receptor-positive breast cancer

- To make a preliminary assessment of the anti-tumor activity of cabozantinib in combination with fulvestrant in patients with metastatic hormone receptor-positive breast cancer

All secondary endpoint analyses of this trial are considered exploratory. A description of each intended analysis is below:

14.4.1 The **ORR** is defined as the proportion of treated patients experiencing a complete response (CR) or a partial response (PR). Patients who begin treatment and do not have a subsequent evaluation will be treated as non-responders. A point estimate for the ORR will be provided, along with a 90% binomial confidence interval.

14.4.2 **OS** is defined as the difference between the date of a patient's enrollment onto this study until the date of death. Patients who are alive at last contact will be censored for OS at this date. An OS estimate will be provided for the overall study population, along with a 90% confidence interval. Kaplan-Meier methodology and Greenwood's formula will be used.

A separate OS analysis will compare patients with bone lesions only to those with bone and soft-tissue lesions. Point estimates with 90% confidence intervals will be provided for each group, and comparisons will be made using a stratified log-rank test.

14.4.3 **PFS** is defined as the difference between the date of a patient's enrollment onto this study until the earlier of the date of progression or the date of death. Patients who are alive and progression-free at last contact will be censored for PFS at this date. A PFS estimate will be provided for the overall study population, along with a 90% confidence interval. Kaplan-Meier methodology and Greenwood's formula will be used.

A separate PFS analysis will compare patients with bone lesions only to those with bone and soft-tissue lesions. Point estimates with 90% confidence intervals will be provided for each group, and comparisons will be made using a stratified log-rank test.

14.4.4 The **effects of cabozantinib on biochemical markers of bone turnover, tumor markers and circulating tumor cells (for participants in cabozantinib/fulvestrant cohort)** will be analyzed at baseline (Cycle 1, Day 1) and on Day 1 of each treatment cycle through the end of study. BAP and NTx levels will be summarized as median (range) and mean (the standard deviation) at baseline and at each time point. Percent change from baseline will be summarized over time. Other bone turnover markers and circulating tumor cells will be summarized similarly.

Tumor markers will be categorized as normal versus abnormal. The proportion of patients with abnormal tumor marker counts will be summarized at baseline and at each time point. Change of tumor marker status from baseline will be tabulated as a two by two contingency table over time.

14.4.5 Skeletal-related event rates will be tabulated and the frequency and proportion of patients experiencing each will be provided. No formal comparisons will be made.

14.4.6 FDG-PET/CT assessment will be described in a qualitative way.

14.5 For the pilot combination cohort of cabozantinib and fulvestrant

14.5.1 Anti-tumor activity will be described in a qualitative way. Bone scan and CT scan response rates, numbers of patients with stable disease and PFS will be reported but these analyses are exploratory only. In similar patient populations, fulvestrant as a single agent has provided PFS times in the range of 3-6 months. (17, 18). These studies did not include patients who had been treated with prior chemotherapies whereas this protocol allows one prior line of chemotherapy and therefore a slightly lower PFS is expected. The combination will be considered promising if it provides PFS of at least 4 months. Bone scan response rates have traditionally not been reported in phase II or III clinical breast cancer trials but as discussed in section 14.1 we believe a response rate in bone of 30% (with associated decreases in patient symptoms) would suggest a combination worthy of further evaluation. The bone response rate will be reported along with a 90% confidence interval. The maximum half-width for this confidence interval will be 19.8%.

We will analyze the safety of fulvestrant and cabozantinib in the first 8 patients enrolled. The table below shows the probability of observing three or more DLTs among the first 8 patients enrolled under different assumed true DLT rates. An exact binomial distribution is assumed:

True DLT rate	Probability of early stopping
0.10	0.038
0.20	0.203
0.30	0.448
0.40	0.685
0.50	0.855
0.60	0.950

Safety Evaluation

Safety analysis will be conducted on the full analysis set (all patients who receive at least one dose of cabozantinib). All AEs occurring on study will be listed by-subject data listing. Type of adverse events (AEs), intensity and incidence rates will be presented by CTCAE grade in all treated participants.

14.6 Reporting and Exclusions

14.6.1 **Evaluation of toxicity**: All participants will be evaluable for toxicity from the time of their first treatment.

14.6.2 **Evaluation of response.** All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

15. PUBLICATION PLAN

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

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17. APPENDICES

18. Appendix A: Cabozantinib dose nomenclature

In other studies using XL184, doses and capsule strengths may be expressed based on the weight of the L-malate salt (Table A1.1). The L-malate salt is also being administered to subjects in this study; however, the convention has been changed such that doses and capsule strengths are expressed based only on the weight of the XL184 freebase. Please note that the salt equivalent weight and thus dose, in these capsules may be slightly higher (Table A1.1).

Table A1.1: Doses for Current Studies (Doses Expressed Based on Freebase Weight)

Freebase Dose (mg)	Salt Equivalent Weight (mg)	As Expressed in previous protocols and IB version 3
100	**126.8**	**125mg dose**
60	**76.0**	**75-mg dose**
39.4	**50.6**	**50-mg dose**
19.7	**25**	**25-mg dose**

In this study the same doses and capsule strengths will be used as in prior and ongoing Cabozantinib studies however;the newer tablet formulation will be used for ease of dosing.

Table A1.2: Equivalent doses of freebase capsules and planned cabozantinib tablets

Freebase capsule dose	Equivalent freebase tablet dose
100mg	**100mg**
19.7mg	**20mg**

Cabozantinib tablet components:

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

19. Appendix B: Modified Response Evaluation Criteria in Solid Tumors Version 1.1

Adapted for this study from Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. (30)

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to the first dose of study treatment. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Non-measurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable. Lymph nodes that have a short axis <10 mm are considered non-pathological and are not be recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion

which can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for non-nodal lesions, shortest axis for measurable malignant nodal lesions).

Non-target lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Bone lesions

- Bone scans must be used to evaluate the bone component of bone lesions, see specific response criteria in

Appendix .

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.

Lesions with prior local treatment

Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

MRI will not be routinely used in this study.

Whole body PET: PET imaging will be used as a secondary endpoint for response assessment in this study.

At each evaluation the current PET results will be categorized by the investigator as described below, with comparators of (1) the baseline PET scan; and (2) the best prior PET scan since (and including) the baseline bone scan:

Response category	**Definition**
Complete Response (CR)	Resolution of all areas of FDG uptake attributable to metastatic disease
Partial Response (PR) *	Significantly decreased FDG uptake in areas attributable to metastatic disease; but not meeting the criteria for CR
Stable Disease (SD)	Not meeting the criteria for CR, PR, PD, or NE
Progressive Disease (PD)[#]	Two or more new areas of FDG uptake attributable to metastatic disease in regions of bone that had not previously shown radiotracer uptake; or unequivocal increase in radiotracer uptake in areas attributable to metastatic disease
Not Evaluable (NE)	Assigned if PET results cannot be interpreted due to inconsistent image acquisition parameters compared to the reference scan, incomplete imaging, or other similar technical deficiencies

Ultrasound: Ultrasound will not be used for response assessment in this study

Tumor Markers: Tumor markers such as CA27.29 or CA153 will be evaluated for changes but will not be used to determine PD in this study.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease will be considered malignant unless cytologically confirmed.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study treatment is delayed or discontinued.

At baseline, tumors and lymph nodes are classified and documented as target or non-target per the definitions provided above. It is possible to record multiple non-target lesions involving the same organ as a single item (eg, 'multiple liver metastases').

At all post-baseline (follow-up) evaluations the baseline classification (Target, Non-Target) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents and CRFs).

For target lesions, measurements should be taken and recorded in metric notation. All tumor measurements must be recorded in millimeters.

At each assessment, a sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported. The baseline sum of the diameters (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for "too small to measure" will be provided on the CRF (a default value of 5 mm will be imputed during analysis).

Non-target lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, a time point response is to be determined for target lesions, non-target lesions, new lesions and overall.

Time Point Response Criteria

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the SoD of target lesions, taking as reference the baseline SoD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Applicable (NA)	No target lesions identified at baseline.
Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD

If the target lesions for a subject meet the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir SoD is 0 (ie, the subject had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR / Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (NA)	No non-target lesions identified at screening
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later).
No	No new lesions present at follow-up
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later).
No	No new lesions present at follow-up
Unable to Evaluate (UE)	Subject not assessed or incompletely assessed for new lesions

Target Lesion TPR	Non-Target Lesion TPR	New Lesions TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/non-PD	No	Non-CR/non-PD
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

* Subjects with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Determining Overall Time Point Response (TPR)

Confirmation

As this is an exploratory phase II study, confirmation of response by repeat assessments performed no less than 4 weeks after the criteria for response are first met will not be required. When reporting the outcome of this study, it will be made clear that the responses were not confirmed. However, the presence or absence of confirmation is not considered when assigning a time point response.

Best Overall Response

Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point.

20. Appendix C: Bone Scan Time Point Response Criteria Per Investigator Assessment

Bone lesions assessed with bone scans at baseline and during follow-up will be documented and evaluated separately, rather than as Non-Target lesions. Bone lesions assessed by other modalities (eg, CT or MRI) are to be documented as Non-Target lesions.

Time Point Response Criteria:

At each evaluation the current bone scan results will be categorized by the investigator as described below, with comparators of (1) the baseline bone scan; and (2) the best prior bone scan since (and including) the baseline bone scan:

Response category	**Definition**
Complete Response (CR)	Resolution of all areas of radiotracer uptake attributable to metastatic disease
Partial Response (PR) *	Significantly decreased radiotracer uptake in areas attributable to metastatic disease; but not meeting the criteria for CR
Stable Disease (SD)	Not meeting the criteria for CR, PR, PD, or NE
Progressive Disease (PD)[#]	Two or more new areas of radiotracer uptake attributable to metastatic disease in regions of bone that had not previously shown radiotracer uptake; or unequivocal increase in radiotracer uptake in areas attributable to metastatic disease
Not Evaluable (NE)	Assigned if bone scan results cannot be interpreted due to inconsistent image acquisition parameters compared to the reference scan, incomplete imaging, or other similar technical deficiencies

[#] Modified from PCWG2 recommendations for establishing time point PD from bone scan evaluation (50)

Asymptomatic bone scan progression as defined above does not warrant study treatment discontinuation. For treatment discontinuation criteria, see Section 5.6

*A caveat to the partial response designation involves the osteoblastic flare phenomenon. Interval visualization of sclerotic lesions of lytic lesions with sclerotic rims, in the setting of other signs of partial response does not indicate disease progression but the healing of previously

inconspicuous lesions. Osteoblastic flare cannot be diagnosed if any preexisting lesions show signs of progression (eg enlargement of lytic lesions, development of new lytic lesions). If flare phenomenon is suspected, other imaging modalities such as CT or plain films may be used to clarify results.

Best Overall Response and Date of Progression

Best overall response and date of progression, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at each time point. For the purposes of determining the date of progression as a result of worsening disease present on bone scan, criteria adapted from PCWG2 recommendations (50) will be applied.

21. Appendix D: Performance Status Criteria

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

22. Appendix E: Pain Questionnaire

11-208 Pain Questionnaire

Participant Name:	
Participant ID number:	**Time Point:**

Please complete on seven consecutive days. Mark answers in pen and answer all questions.

Day 1
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:
   - ☐ Very much worse
   - ☐ Moderately worse
   - ☐ A little worse
   - ☐ About the same
   - ☐ A little better
   - ☐ Moderately better
   - ☐ Very much better

Day 2

Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 3
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 4
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 5
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 6
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 7
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Patient signature:_____ **Date:** _____

23. Appendix F: Suggested algorithm for management of treatment-related diarrhea

Diarrhea Event Based on NCIC CTC v4.0	**Action**
Grade 1	• Take loperamide 4mg at the first onset of diarrhea and then

Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	2mg every 4 hours or after each loose stool until the subject is diarrhea –free for at least 12 hours. During the night the subject may take 4mg loperamide every 4 hours. (up to a maximum daily dosing of 16mg) • Continue cabozantinib • Fluid intake of ~2L should be maintained to avoid dehydration. • Follow dietetic recommendations (see text below).
Grade 2 Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	• Take loperamide as above. Continue investigational product. If diarrhea has not improved to ≤ grade 1 within 24-48 hours despite optimal medical therapy, hold cabozantinib until grade 1 and then resume at the same dose. If grade 2 diarrhea recurs, resume at one dose level lower.* • Fluid intake of ~2L should be maintained to avoid dehydration. • Follow dietetic recommendations (see text below). • Monitor closely and consider intravenous hydration.
Grade 3 Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	• Take loperamide as above. Hold the investigational product until recovery to ≤ grade 1 and then resume at one dose level lower. If diarrhea recurs, hold again until recovery and again reduce by one dose level. * • Fluid intake of ~2L should be maintained to avoid dehydration. • Follow dietetic recommendations (see text below). • Consider octreotide or other management of diarrhea (see text below) • Consider hospitalization if no improvement of the diarrhea within 24 hours.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Permanently discontinue investigational product. • Fluid intake of ~2L should be maintained to avoid dehydration. • Follow dietetic recommendations (see text below). • Consider octreotide or other management of diarrhea (see text below) • Consider hospitalization if no improvement of the diarrhea within 24 hours.

* See section 6.3 for dose levels.

Dietetic Measures:

- Stop all lactose-containing products
- Drink 8-10 large glasses (approx. 2 Liters) of clear liquids per day
- Eat frequent small meals
- Recommend low fat regimen enriched with bananas, rice, applesauce and toast (BRAT diet)

Additional Medical Management:

- Loperamide is the recommended standard therapy to treat diarrhea in this study.
- Other agents that may be used include diphenoxylate hydrochloride and atropine sulfate formula or diluted tincture of opium as described by Benson et al. (46)
- Administer octreotide [100-150μg SC BID or IV (25-50 μg/h) if dehydration is severe, with dose escalation up to 500 μg TID)]
- Use intravenous fluids as appropriate
- Consider prophylactic antibiotics (eg fluoroquinolones), especially if diarrhea is persistent beyond 24hours or there is fever or grade 3-4 neutropenia.

Stool cultures should e done to exclude infectious causes of grade 3 or 4 diarrhea or diarrhea of any grade with complication features (dehydration, fever, and/or grade 3 or 4 neutropenia) per the investigator's discretion.
Documentation of any occurrences of loose stools or diarrhea must be as precise as possible. Documentation of 'intermittent' events of diarrhea is limited to grade 1. If events of grade 1 diarrhea are separated by 3 days without any diarrhea, then each event must be documented as separate adverse events with corresponding start and stop dates.

DFCI IRB Protocol #: 11-208

APPENDIX G

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations; Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CHB, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.). The Lead Institution is the home of the Overall PI.

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A Participating Institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The Participating Institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center

Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

Clinical Trials Office: The clinical trials offices of the DF/HCC consortium members support investigators and their study teams with the coordination, submission and ongoing conduct of research protocols involving human subjects. Specifically, these offices support four core service areas including; pre-review of PI initiated protocols; assistance in the preparation and management of Investigational New Drug (IND) applications and subsequent required reporting to the FDA; regulatory consultation and guidance in the interpretation of local, federal, and ICH/GCP guidelines and policies; and the orientation and ongoing training support of clinical research personnel.

DF/HCC Quality Assurance Office for Clinical Trials: The DF/HCC QACT is a unit that has been developed to computerize, manage, and QC & QA data and DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to audit DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair, Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Steven Isakoff, MD, PhD, will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling subjects.
- For international trials, assure that the protocol is provided to Participating Institutions in the primary language spoken at the site.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.

- Act as the single liaison with FDA as applicable.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution, Massachusetts General Hospital Cancer Center, will ensure that all Participating Institutions within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of FWA and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain FDA correspondence as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute Serious Adverse Event safety reports (both IND Safety reports and protocol specific SAEs).
- Monitor at Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Verify that eligibility has been confirmed by the investigator and that appropriate consent has been obtained.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

Each Participating Institution will provide to the Coordinating Center a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.

The general responsibilities for each Participating Institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event reports to local IRB and directly to the Coordinating Center. For CTEP trials, submit SAE reports directly to CTEP and provide copies to the Coordinating Center
- Submit deviations and violations to local IRB and the Coordinating Center.
- Secure investigational agents per federal guidelines and protocol requirements.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company)

3.0 PROTOCOL DEVELOPMENT

3.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and if applicable FDA Guidelines. Further, the Protocol Chair will be the single liaison with the FDA as applicable.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify, qualify and initiate Participating Institutions and obtain accrual commitments.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

3.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Maintain Regulatory documents for all Participating Institutions.
- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all Participating Institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all Participating Institutions (conference call, emails, etc)
- Maintain documentation of all communications.

4.0 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Coordinating Center must maintain copies of all IRB approvals, for each Participating Institution.

4.1 Protocol Distribution

The Coordinating Center will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

4.2 Protocol Revisions and Closures

The Participating Institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating Institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol Closures and Temporary Holds: Participating Institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

4.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent from participating institutions. As best a possible, the template should be followed with the specifications outlined in the DF/HCC guidance document on Model Consent Language.

Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Lead Site for their revision prior to submission to the participating site's IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. **It is DF/HCC policy that only attending physicians can obtain informed consent and re-consent to drug and/or device trials.**

4.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee and must be submitted and approved by the DFCI IRB prior to participant registration:

- Approval Letter of the institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution’s IRB
- IRB approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the DF/HCC Lead Institution their IRB approval for Amendments to a protocol.

4.5 IRB Re-Approval

Annual IRB re-approval from the Participating Institution is required in order to continue research and register participants onto a protocol. There is no grace period for continuing approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution from the Participating Institutions on or before the anniversary of the previous approval date.

4.6 Participant Confidentiality and Authorization Statement

The HIPPA of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol, the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol Participating Institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

4.7 Participant Registration and Randomization

To register a participant, please refer to Section 4.4 of the protocol, Registration Process for Other Participating Institutions.

4.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

4.9 DF/HCC Multi-center Protocol Registration Policy

4.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy**.**

4.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

4.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

4.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

4.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study. *Note: It is necessary to send only ONE copy of all paper Case Report Forms, if applicable.*

4.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)

1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

If a time frame is not specified in the protocol, tests must be completed as follows:

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the QACT.
- For protocols requiring measurable disease, lab baseline measurements must be completed within 14 days prior to study enrollment by the QACT. Examples: flow cytometry, HLA typing, fluid cytology, tumor markers and hormones (CEA, CA-27-29, CA-125).
- Non-lab tests required for eligibility must be performed within 30 days prior to study entry. Example: radiological scans
- For bone marrow transplant (BMT) protocols and non-protocol treatment plans, eligibility tests must be completed within 42 days prior to enrollment by the QACT. The extended period of time is allowed to facilitate insurance approval while ensuring participant safety.

4.10.2 On-study Form(s)

Purpose - documents the following items:

- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

4.10.3 Baseline Assessment Form(s)

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.10.4 Treatment Form(s)

Purpose - Records the following information related to the time the participant receives protocol treatment:

- Participant, Protocol information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

4.10.5 Adverse Event Report Form(s)

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. *This form is not for IRB submission, but for recording the AE in the research database.*

4.10.6 Response Assessment Form(s)

Purpose – Documents objective and subjective response as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.10.7 Off Treatment and Off Study Form(s)

Purpose - The Off Treatment and Off Study Forms are submitted when the participant is
removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol**,** the Off Study Form is the last form submitted.

4.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

4.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Completeness:
Is all the information provided as required per protocol?

Protocol Treatment Compliance:
Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

4.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

5.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol.

Participating Institutions should order their own agent regardless of the supplier (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB. If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state, federal, and good clinical practice guidelines. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

6.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

6.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

6.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol, Section 11.2. This trial will assess adverse events and serious adverse events utilizing the NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

The Lead Institution will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating all SAEs to all sites conducting the trial.

Participating Institutions must report the AEs to the Protocol Chair and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

6.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The Protocol Chair will review all IND Safety Reports and is ultimately responsible for forwarding the IND Safety Reports to the Participating Institutions. The Participating Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

7.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all Institutions Participating in the DF/HCC Multi-center Protocol.

7.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

7.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations.

The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the Participating Institution's own IRB, per its institutional policy.

A copy of the Participating Institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

8.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality control oversight for the DF/HCC Multi-center Protocol.

8.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Eligibility verification will be performed for all external participants prior to official registration with QACT and study enrollment. The DF/HCC study coordinator will review the source documentation required for registration, as outlined in protocol Section 4.4. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

The DF/HCC Lead Institution will implement virtual monitoring activities ongoing to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. The DF/HCC study coordinator will routinely review the electronic data capture system to monitor external site data entry progress and compliance with protocol requirements. Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information that may include: Participation in regular Lead Institution initiated teleconferences, ongoing email updates highlighting overall protocol progress and important announcements, and collecting source documents from Participating Institutions, at specific data points, that support the primary and or secondary endpoints.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair.

8.2 Evaluation of Participating Institution Performance

8.2.1 Eligibility Checklist:

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

8.2.2 Accrual of Eligible Participants:

Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials are calculated for each institution. Participating Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. The main focus in auditing is to measure if the standards and procedures set are being followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the Code of Federal Regulations.

9.1 DF/HCC Sponsored Trials

Each participating site will be scheduled for an audit within the first 12 months of activation at the site provided that at least 2 participants have been enrolled. The DF/HCC QACT will conduct source verification for the selected participants that will be audited. If the audit reveals violations that impact participant safety and/or the integrity of the study data, additional participant records may be audited at a later date. The QACT may also choose an unannounced record to be reviewed during a scheduled audit. Each site may also be re-audited prior to the study closure.

The participating institutions may be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the participating institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

9.2 Participating Institution

It is the Participating Institution's responsibility to notify the DF/HCC Lead Institution of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair and the DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and

compliance with state, federal, and Good Clinical Practice guidelines, will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

Appendix I - CYP 450 Clinically Significant Drug Interaction Table

INHIBITORS			
1A2	**2B6**	**2C8**	**2C19**
cimetidine fluoroquinolones fluvoxamine ticlopidine	thiotepa ticlopidine	gemfibrozil montelukast	fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole ticlopidine
INHIBITORS			
2C9	**2D6**	**2E1**	**3A4,5,7**
amiodarone fluconazole isoniazid	amiodarone bupropion chlorpheniramine cimetidine clomipramine duloxetine fluoxetine haloperidol methadone mibefradil paroxetine quinidine ritonavir	disulfiram	HIV Protease Inhibitors: indinavir nelfinavir ritonavir amiodarone azithromycin cimetidine clarithromycin diltiazem erythromycin fluvoxamine itraconazole ketoconazole mibefradil nefazodone troleandomycin verapamil
INDUCERS			
1A2	**2B6**	**2C8**	**2C19**
Tobacco	phenobarbital phenytoin rifampin	N/A	N/A
INDUCERS			
2C9	**2D6**	**2E1**	**3A4,5,7**
rifampin secobarbital	N/A	Isoniazid	carbamazepine phenobarbital phenytoin rifabutin rifampin St. John's wort Troglitazone

A more complete list can be found in http://medicine.iupui.edu/clinpharm/ddis/table.asp

24. Appendix J: Instructions for pharmacokinetic sampling

Pharmacokinectic samples may be taken as per institutional standard of care at the protocol specified times. Blood samples may be drawn peripherally or via an indwelling central venous catheter where applicable. Specific instructions are detailed below.

Place a large gauge peripheral catheter (e.g., 19 or 20 gauge angiocath straight set with T-connector, or similar IV access device) within a vein in the arm of the patient, for the collection of pharmacokinetic blood samples on day 15. Patency of the sampling catheter should be maintained between blood draws using either a heparin lock (e.g., 10 U/mL in normal saline) or a slow drip of Normal Saline for Injection, USP (e.g., 10 mL/h). Blood may be obtained directly by venipuncture on day 16 when only a single pharmacokinetic blood specimen is scheduled for collection. When sampling through the peripheral catheter, begin to clear the catheter approximately 1 min before the specified sample time by withdrawing the lock solution and approximately 0.5 mL of blood into a syringe. Remove and properly dispose the syringe used to clear the catheter.

A battery-powered digital timer/stopwatch programmed to operate continuously as a 24-h clock must be used to accurately monitor the drug administration and sample collection times. The same timer must be allowed to run without interruption until the last pharmacokinetic blood specimen has been obtained from the subject. Timer readings will be noted at the precise time that the infusion is started and ended, as well as at the beginning and ending times of the blood sample collection intervals. Readings of the digital timer must be directly recorded on a copy of the Pharmacokinetic Data Form for this study. Computer files for printing the Pharmacokinetic Data Form and sample collection and storage tube labels will be sent to each site.

Blood samples (6 mL) will be obtained shortly before taking the day 15 dose of cabozantinib and at 0.5h(± 15 min), 1.0h(± 15 min), 2.0h(± 15 min), 3.0h(± 15 min), 4.0h(± 30 min), 6.0h(± 30 min), 8.0h(± 30 min), and 24.0 h(± 1 h) [must be drawn prior to administration of dose 2] after dosing. It is very important that the patient is aware that the morning dose of cabozantinib on day 16 must not be taken before arriving at the clinic and the 24.0 h pharmacokinetic sample has been collected.

Samples are to be collected in a plastic green stoppered Vacutainer 6.0 mL plasma collection tube with spray-coated sodium heparin (Becton-Dickinson, cat. no. 367878). Promptly mix the plasma collection tube by gently inverting it 5-times, then place it on wet ice until centrifuged (1,300 x g, 10 min, 4°C) within 15 min after collection. Separate the plasma from the blood cells using a disposable pipet and transfer the plasma into a 4.5 mL self-standing polypropylene cryogenic storage vial with external threads (Fisher Scientific, cat. no. 12-565-291). Affix a pre-printed label, with the protocol number, patient accession number, sample number, collection date, and desired time onto the cryovial, oriented crosswise toward the upper part of the tube, without overlapping the vial cap. Completely cover the label with polyester protective label tape (Fisher Scientific, cat. no. 11-867B); otherwise, labels are prone to separate from the vial when packed in dry ice for shipment. Place the tube on crushed dry-ice until stored in a freezer maintained at < -70°C.

Complete sets of samples from one or more patients should be sent by overnight mail to the address listed below. Place the sample tubes in a zip lock plastic bag. Package samples in a seamless styrofoam container. Place the sample bag over at least 3 inches of dry ice on the bottom of the container and completely cover with an additional 3 inches or more of dry-ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Insert copies of the Pharmacokinetic Data Form for each set of samples into a separate zip-lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Send the samples from Monday to Wednesday by overnight courier for delivery by 10 a.m. on the following day. Samples should not be shipped on a Thursday or Friday. Please provide notification of the sample shipment by e-mail prior to shipping to Dr. Supko (jsupko@partners.org) and Sarah Hilderbrand (e-mail: slhilderbrand@partners.org).

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

Appendix K: Procedure for Collecting and Shipping Circulating Tumor Cells (CTCs)

Circulating tumor cells (CTCs) will be processed via the semi-automated CellSearch^{R} processing technique (Veridex). Briefly, 7.5 ml of whole blood is collected in CellSave^{R} preservative tubes. Samples can sit at room temperature for up to 96 hours.

SAMPLE COLLECTION

1. Do not draw samples within 7 days of doxorubicin administration.
2. Sample must be collected in CellSave^{R} preservative tubes. Label tubes with the sample identifier/number, protocol number, and submitting investigator.
3. Collect at least 8 ml of blood per sample. Gently invert the tube 8 times to prevent clotting immediately after filling the tube.
4. Do not submit clotted samples.

SAMPLE SHIPPING FOR DF/HCC SITES

1. Samples should be stored and transported at room temperature (15-30C) until processing. Do NOT refrigerate or freeze the sample.
2. Samples must be processed WITHIN 96 hours of collection, but best results are obtained if the sample is processed as soon as possible.
3. Overnight ship samples **AT ROOM TEMPERATURE** to:

Dr. Alarice Lowe/Paula Rosenthal
Brigham and Women's Hospital
75 Francis Street
Medical Research Building, Room 309
Boston, MA 02115
Tel: 617-732-4715
Fax: 617-582-6015
Email: aclowe@partners.org

CTC samples are processed Monday through Friday.
Samples drawn on Thursday MUST be sent immediately for processing. Samples should NOT be drawn the day before a long weekend.

SAMPLE SHIPPING FOR MSKCC

The tubes are to be kept at room temperature and shipped to the MSKCC Clinical Chemistry Research Laboratory.

Mail at ambient temperature to:
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
Biomarker Laboratory, Howard 359
N.Y., N.Y. 10065

OTHER MEDICATIONS TAKEN

If you take a **new** daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Drug Name	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Participant Identifier: _____
Protocol # : 11-208
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Cabozantinib
How Much: Your dose is _____
How Often: You will take each dose once a day in the morning
When: At approximately the same time each day

SPECIAL INSTRUCTIONS:

1. Complete one form for each cycle (cycle = 21 days).
2. Do not eat 2 hours prior to taking cabozantinib. You may drink water.
3. Swallow tablets whole with 8 oz. of water. Continue to fast for 1 hour after each dose of cabozantinib.
5. If you miss or vomit a dose, do not take another one.
6. Any missed or vomited doses should be reflected in this diary. Record the date,the number of tablets you took, and when you took them.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your research doctor when you go for your next appointment

DOSING LOG

Cycle: ___

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken	Comments
Ex:	6/1/2009		vomited pill
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

11-208: Pain Medication Diary

Subject Name: _____

To be completed by study site

Subject ID: __ __ __ __ - __ __ __ __ Assessment Period: ☐ Screening ☐ Study Week: ___ ___

Instructions:

Please complete this diary during the 7-day period that you complete the Daily Pain Questionnaire.

- At the beginning of each 7-day period, describe each type of pain medication you are taking by writing in the medication name, route, and strength in the columns below.
- List only one type of medication on each row. Include all the medications you are taking for pain, even if you are not certain the medication is for treating pain.
- During this 7-day period, if you start a new medication or change the strength of the pills, write the new information on a new row. (Do not change the information about the medication you have already taken)

Daily Medication Use

- Each day, record the number of units you take of each medication.
- If not provided by your study site, write in the day's date where indicated (Month/Day/Year).

Medication Name (write in name)	**Route** (check one box)	**Strength** (example: 50 mg)	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken	**Date:** __/__/__ *(mm/dd/yy)* # Taken
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
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	☐ Pill ☐ Patch ☐ Injection								
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	☐ Pill ☐ Patch ☐ Injection								

PROTOCOL NUMBER:
XL184-Investigator Sponsored Trial (IST)/
Cancer Therapy Evaluation Program (CTEP)

PHARMACY MANUAL

Investigational Product Main Distributor:	**Exelixis Inc.** **210 East Grand Avenue** **South San Francisco, CA 94083**
Study Drug:	**Cabozantinib (XL184) Tablets**
IND Number:	**72,596**

Version 2.0
08 August 2012

All queries regarding investigational product (IP) shipments should be directed to Exelixis Clinical Supplies at Clinical_Supplies@Exelixis.com

This Pharmacy Manual provides instructions to help you understand the management of the investigational product (IP), cabozantinib. This manual should be stored in the Pharmacy Binder, at the same location where IP is stored.

Detailed instructions on the management of IP are also included in the protocol. You are encouraged to read both this manual and the protocol closely before the study commences at your site and refer to them whenever a new study subject is enrolled.

An initial supply of IP will be shipped to your site following regulatory approval and activation by Exelixis.

Protocol XL184-IST/CTEP

PHARMACY MANUAL

Table of Contents

INSTRUCTIONS FOR THE INVESTIGATIONAL PRODUCT MANAGER

1 SITE PERSONNEL RESPONSIBILITIES

The Principal Investigator (PI) should assign responsibility for the investigational product (IP) management to one primary study staff member. This person must be a licensed healthcare professional, preferably a pharmacist or a nurse. This manual will refer to this person as the Investigational Product Manager (IPM). It is recommended that a back-up person also be identified to cover in the absence of the primary IPM.

2 STUDY DESCRIPTION

Please refer to the Investigator Sponsored Trial (IST)/Cancer Therapy Evaluation Program (CTEP) protocol.

3 INVESTIGATIONAL PRODUCT DESCRIPTION AND PACKAGING

Exelixis will provide approved investigative sites with adequate supplies of IP.

3.1 Cabozantinib (XL184)

Cabozantinib is supplied as 60 mg and 20 mg yellow film-coated tablets. The 60 mg tablets are oval shaped and the 20 mg tablets are round. The components of the tablets are listed in the following table:

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

Refer to the Investigator Brochure for additional information on Cabozantinib.

3.1.1 Cabozantinib (XL184) Packaging

IP (Cabozantinib -XL184) will be provided in bottles containing 25 tablets or 30 tablets each.

4 STORAGE AND HANDLING

All IP must be stored in a secure location with access available only to authorized personnel. The IP must be stored at controlled room temperature (20-25 degrees Centigrade, or 68-77 degrees Fahrenheit); allowing for excursions between 15 and 30 degrees Centigrade (59 and 86 degrees Fahrenheit) and inventoried according to applicable state and federal regulations.

Subjects need to be instructed to:

- Return all IP to the study site for drug accountability and disposal. This includes fully used, partially used, unused, damaged, and expired IP.
- Store the IP at controlled room temperature, away from direct sunlight or appliances/items that give off heat, and out of reach of children and/or pets.
- Not store the study drug in a hot, unventilated car for a long period of time.

5 ANCILLARY SUPPLIES

No ancillary supplies relating to drug product will be distributed or used in this study.

6 DRUG SHIPMENTS

6.1 Initial Shipments

After IST or CTEP site activation, the site is required to submit the completed initial drug supply request form by email to Clinical_Supplies@Exelixis.com.

NOTE: If necessary, drug supply request forms can be requested from Exelixis Clinical Supplies.

6.2 Re-Supply Requests

Subsequent shipments of all IP will be made following submission of a drug supply request form to Exelixis Clinical Supplies.

All drug supply request forms must be fully completed by filling in the Exelixis IST or CTEP study number, drug requested with quantity, expected date of delivery at site, and signature and date.

6.3 Shipment Requests and Timelines

General drug shipments will take place Monday through Wednesday only. In case of emergency, a special request will need to be authorized by Exelixis Clinical Supplies in order to ship on Thursday and/or Friday. If a special drug shipment request is needed, please contact Exelixis Clinical Supplies immediately.

6.4 Drug Re-Test and Expiry Date

Exelixis maintains an on-going stability program for all lots of cabozantinib being used in study trials. Exelixis is responsible for and has processes regarding the management of retest dates for cabozantinib supplied. All documentation should be filed in the site Pharmacy Binder.

6.5 Drug Receipt and Confirmation

The IPM (pharmacist or assigned designee) is responsible for proper inspection of each shipment of IP received. At the time of receipt, the IPM must confirm all supplies are intact and in good condition.

Once IP is received in good condition, write in the IST or CTEP study number on the designated blank line available on the label of the IP bottle(s). The IST or CTEP study number can be found on the site's drug supply request form.

If a bottle is missing or damaged, please notify Exelixis Clinical Supplies immediately. Do not dispense the IP unless otherwise notified by Exelixis Clinical Supplies.

The site is responsible for ensuring proper maintenance of all IP shipment/receipt documentation.

NOTE: If there are any issues with IP shipments, please notify Exelixis Clinical Supplies immediately. Exelixis will use information obtained from you to determine if the IP is still acceptable for use. Once a final decision is made regarding the disposition of any IP placed

on a quarantine status, you will receive further information regarding the availability or unavailability of the IP.

7 INVESTIGATIONAL PRODUCT DISPENSATION/ADMINISTRATION

7.1 Dispensation and Administration

7.1.1 Cabozantinb Dispensation

All cabozantinib should be dispensed in the original container supplied by Exelixis and should not be repackaged unless unavoidable. If cabozantinib is repackaged, cabozantinib is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

7.1.2 Cabozantinib Administration

Subjects should receive cabozantinib tablets daily at approximately the same time each day.

Upon completion of a 2-hour fast, the subject should receive the dose of cabozantinib with a minimum of 8 oz/240 mL of water and then continue to fast for 1 hour. Following the required fast the subject should be allowed to eat.

7.2 Instructions on Dose Reduction and/or Hold

Refer to the IST or CTEP protocol for further details on dose reduction and dose holds.

7.3 Subject Dosing Instructions

Refer to Section 7.1.2 of this document for out-patient dosing instructions. Subject compliance with out-patient study treatment regimens will be assessed by the site using standard procedures.

8 RECORD KEEPING

All records must be retained and available per site procedures. At the end of the study, the IP records may be incorporated into the clinical study file for long-term storage. The site is responsible for maintaining the study documents for at least 2 years after cabozantinib receives marketing approval for the indication being investigated, or 2 years after formal discontinuation of clinical development of cabozantinib and FDA notification of such (ie, the IND is closed), or until further notification from Exelixis.

8.1 Investigational Product Accountability Procedures

The investigator or IPM is required to maintain accurate IP accountability records per site procedures. Study subjects should be instructed to return all IP to the study site for drug accountability and disposal. This includes fully used, partially used, unused, damaged, and expired IP. If your site does not have an SOP for proper destruction of IP, please contact Exelixis Clinical Supplies for further instructions. No IP should be returned to Exelixis.

9 INVESTIGATIONAL PRODUCT DISPOSITION

As deemed necessary by Exelixis, follow your site SOP for destruction of IP. A copy of your destruction SOP should be provided to Exelixis Clinical Supplies for review, approval and before any IP can be destroyed at your site. If no SOP is in place at your site, Exelixis Clinical Supplies will provide you the necessary instructions for destruction of IP. This includes fully used, partially used, unused, damaged, and expired IP. At no time during the study should IP be returned to Exelixis.

10 PHARMACY MANUAL HISTORY

Pharmacy Manual Version	Effective Date	Change Summary
2	08 August 2012	Revised Version

OTHER MEDICATIONS TAKEN

If you take a **new** daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol # : 11-208
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Cabozantinib
How Much: Your dose is _____
How Often: You will take each dose once a day in the morning
When: At approximately the same time each day

SPECIAL INSTRUCTIONS:

1. Complete one form for each cycle (cycle = 28 days).
2. Do not eat 2 hours prior to taking cabozantinib. You may drink water.
3. Swallow tablets whole with 8 oz. of water. Continue to fast for 1 hour after each dose of cabozantinib.
5. If you miss or vomit a dose, do not take another one.
6. Any missed or vomited doses should be reflected in this diary. Record the date,the number of tablets you took, and when you took them.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your research doctor when you go for your next appointment

DOSING LOG

Cycle: ___

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken	Comments
Ex:	6/1/2009		vomited pill
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

[Insert institution letter head here]

[Insert Date Here]

[Click **here** and type recipient's address]

Dear Ms. [insert name here],

Thank you for your participation in the *Phase II Trial of Cabozantinib in Women with Metastatic Hormone-Receptor-Positive Breast Cancer with Involvement of Bone* at [insert institution name here]. We are writing to inform you of a change in the frequency of follow up for this clinical trial.

Previously, we planned to keep track of each participant's medical condition annually for 5 years. We now plan to contact participants via telephone every six months for the first two years following completion of study treatment and once a year thereafter to see how they are doing. During the remaining 3 years of follow-up, if you are still being treated at (insert institution name), we will review your medical records. If you are no longer being followed by a doctor at our institution, we will contact you by phone to see how you are doing. Keeping in touch with you and checking your condition every year helps us look at the long-term effects of the research drug cabozantinib.

Please contact [insert team member and title] at [insert phone number] if you should have any questions or concerns regarding this change. Thank you for your continued participation in this important research study.

Respectfully,

[Insert Investigator Name/Co-investigator name here and title]

11-208 Pain Questionnaire

Participant Name:	
Participant ID number:	**Time Point:**

Please complete on seven consecutive days. Mark answers in pen and answer all questions.

Day 1
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 2
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 3
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 4
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 5
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 6
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Day 7
Date:_____

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my pain in the last 24 hours was:

- ☐ Very much worse
- ☐ Moderately worse
- ☐ A little worse
- ☐ About the same
- ☐ A little better
- ☐ Moderately better
- ☐ Very much better

Patient signature:_____ **Date:** _____

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**11-208**
Protocol Name:	**A Phase II trial of cabozantinib in women with metastatic hormone-receptor-positive breast cancer with involvement of bone**
DFCI Site PI:	Sara Tolaney, MD
DFCI Research Nurse:	Peg Haldoupis, RN; Liz Kasparian, RN; Mary O'Driscoll, RN; Kathy Roche, RN; Myra St. Amand, RN, Beth Tiani, RN

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
*** Remember to check the ALERT PAGE***

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	***Cabozantinib*** inhibits multiple receptor tyrosine kinases (RTKs) with growth-promoting and angiogenic properties. ***Study Design*** - See Section 1.1; ***Study Rationale*** – See Sections 2.5 – 2.6. A cycle will be defined as 21 days in the main study and 28 days in the fulvestrant/cabozantinib combination cohort – Section 5.
Dose Calc.	• Cabozantinib and fulvestrant are both flat/fixed dosing in mg – Section 5.0
Study Drug Administration	***Cabozantinib*** – Sections 5 and 7 • Oral, taken on a continuous once daily dosing schedule. • Must fast for 2 hours before and 1 hour after dosing. • Should be taken in the morning will a full glass of water (minimum 8oz/240mL). • Missed and vomited doses will not be made up. ***Fulvestrant*** – Section 5 and 7 • Intramuscularly (IM) in clinic on Days 1 and 15 of Cycle 1, then on Day 1 of each subsequent cycle. • Must be administered intramuscularly in the buttocks slowly (1-2 minutes per injection) as two 5-ML injections (one in each buttock) – See Section 5.2.1 for details. **NOTE:** Pre-treatment criteria for Cycle 1, Day 1 is in Section 5.1
Dose Modifications & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 6.0 • This protocol uses NCI CTCAE criteria, version 4.0 – Section 2.8 • Definition of a DLT for fulvestrant/cabozantinib cohort is in Section 2.8 • Table 6-1: Non-heme toxicities management • Table 6-2: Heme toxicities management • QTc prolongation – See Section 6.4.10 • Toxicity management – Section 6.4 • Dose modifications/delays – Section 6.5 • Dose reductions for fulvestrant/cabozantinib cohort – Section 6.6
Con Meds	*Concomitant Therapy* Guidelines are in Section 5.3 and Appendix I • Please review Section 5.3 and Appendix I for permitted, prohibited and "use with caution medications" • PPIs, H2 blockers and antacids should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib & but least 14 hours before the next dose of cabozantinib if possible.
Required Data	*Study Calendar and Assessment Required data* are outlined in Sectiona 8 and 9 (Study Calendar) • PKs are only for first 8 participants in the fulvestrant/cabozantinib cohort – See Section 8.1 and Appendix J
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to also DOCUMENT any additional vital signs, routes of administration, IM injection sites for fulvestrant and EXACT times of PK collection.