Status Page

PROTOCOL 14-359

Permanent
Closed to New Accrual

Closure Effective Date: 06/11/2018
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: ***10/23/2017***

Alert Page

DF/HCC Protocol #: **14-359**

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

Protocol Section 2.7.6, Section 9.7, Section 10, and Appendix F: The research blood draw for cfDNA will occur at baseline and at end of treatment. [Amendment forthcoming]

Protocol Section 10: The research blood draw for Plasma biomarkers should occur at baseline, C1D8, C2D1, C3D1, C4D1, C5D1, C6D1 and then every 2 cycles, and at end of treatment. [Amendment forthcoming]

Protocol Section 10: If the research blood draws are not performed at screening then it can be collected on C1D1 prior to the start of treatment. [Amendment forthcoming]

Protocol Section 5.2: Urine protein / creatinine ratio (UCPR) is collected at the start every odd cycle beginning C3D1. The UCPR from odd cycles may be used as the criteria to treat on even cycles.

Protocol Version/Date: Version 9/ July 17, 2017

NCI Protocol *#: N/A*

Local Protocol #: 14-359

Title: A Phase II study of cabozantinib alone or in combination with trastuzumab in breast cancer patients with brain metastases

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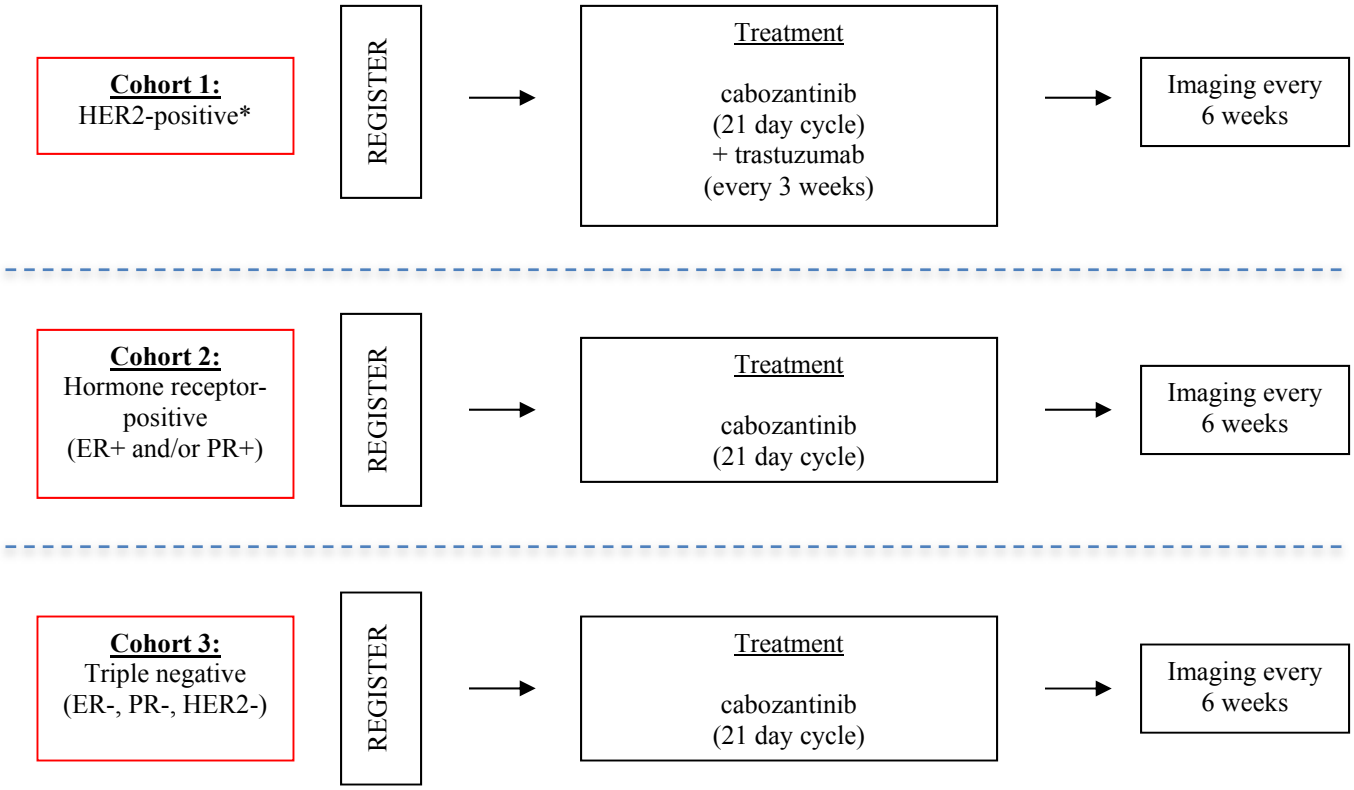
Agent(s): *Cabozantinib (NSC #; IND# 116866)*

SCHEMA



Eligibility:
Metastatic breast cancer
New or progressive CNS lesions, one of which must be measurable

* Accrual will be paused when 6 patients have received first doses of cabozantinib and trastuzumab in this cohort (see section 5.3 for safety evaluation)

TABLE OF CONTENTS

SCHEMA **3**

1. OBJECTIVES **8**

1.1 Study Design *8*

1.2 Primary Objectives *8*

1.3 Secondary Objectives *8*

2. BACKGROUND **9**

2.1 Cabozantinib *9*

2.2 Cabozantinib Nonclinical Toxicology *10*

2.3 Clinical Experience of cabozantinib *11*

2.4 Trastuzumab *16*

2.5 Brain Metastases in Breast Cancer *18*

2.6 Rationale *18*

2.7 Correlative Studies Background *22*

3 PARTICIPANT SELECTION **24**

3.1 Inclusion Criteria *24*

3.2 Exclusion Criteria *28*

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations *31*

4 REGISTRATION PROCEDURES **31**

4.1 General Guidelines for DF/HCC and DF/PCC Institutions *31*

4.2 Registration for DF/HCC Institutions *32*

5 TREATMENT PLAN **33**

5.1 Treatment Overview *33*

5.2 Pre-treatment Criteria *35*

5.3 Initial Safety Evaluation of cabozantinib + trastuzumab *36*

5.4 Agent Administration *38*

5.5 General Concomitant Medication and Supportive Care Guidelines *39*

5.6 Potential Drug Interactions *40*

5.7 Compliance *42*

5.8 Study Drug Accountability *43*

5.9 Duration of Therapy *43*

5.10 Duration of Follow Up 44
5.11 Criteria for Removal from Study 44

6 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS DUE TO CABOZANTINIB 45
6.1 Anticipated Toxicities 45
6.2 Dose Modifications/Delays and Toxicity Management 45
6.3 Management of Adverse Events 46

7 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS DUE TO TRASTUZUMAB 65
7.1 Recommendations for Dose Modification of Trastuzumab Based on Cardiac Monitoring 65
7.2 Management of Acute Infusion Syndrome 66

8 DRUG FORMULATION AND STORAGE 67
8.1 Cabozantinib 67
8.2 Trastuzumab 69

9 CORRELATIVE / SPECIAL STUDIES METHODS 70
9.1 Evaluate c-Met and phosphor-c-Met expression in FFPE tumor tissue (and optional baseline tumor biopsies, if available) 70
9.2 Evaluate the incidence of c-Met positive circulating tumor cells at baseline 70
9.3 Evaluate potential plasma biomarkers of cabozantinib 71
9.4 Cerebral blood volume, blood flow, vessel size, tumor infiltration 72
9.5 Pain Assessments 73
9.6 Tumor biopsies 74
9.7 Blood sample collection 74

10 STUDY CALENDAR 76

11 MEASUREMENT OF EFFECT 80
11.1 Definitions 80
11.2 Disease Parameters 80
11.3 Methods for Evaluation of Measurable Disease 82
11.4 Response Criteria 84
11.5 Neurological Signs and Symptoms (NSS) 89

12 ADVERSE EVENT REPORTING REQUIREMENTS 90

12.1 Definitions ... *90*
12.2 Procedures for AE and SAE Recording and Reporting ... *92*
12.3 Expedited SAE Reporting Guidelines ... *93*
12.4 Reporting to the Institutional Review Board (IRB) ... *94*
12.5 Reporting to the Food and Drug Administration (FDA) ... *94*
12.6 Reporting to the Hospital Risk Management ... *95*
12.7 Monitoring of Adverse Events and Period of Observation ... *95*

13 DATA AND SAFETY MONITORING ... 95
13.1 Data Reporting ... *95*
13.2 Safety Meetings ... *96*
13.3 Monitoring ... *97*

14 REGULATORY CONSIDERATIONS ... 97
14.1 Protocol Review and Amendments ... *97*
14.2 Informed Consent ... *97*
14.3 Ethics ... *98*
14.4 Study Documentation ... *98*
14.5 Records Retention ... *99*

15 STATISTICAL CONSIDERATIONS ... 99
15.1 Study Design / Endpoints ... *99*
15.2 Sample Size / Accrual Rate ... *99*

16 PUBLICATION PLAN ... 102

REFERENCES ... 103

APPENDIX A: PERFORMANCE STATUS CRITERIA ... 107

APPENDIX B: PAIN QUESTIONNAIRE ... 109

APPENDIX D: PARTICIPANT'S MEDICATION DIARY ... 112

APPENDIX E: NEUROLOGICAL SIGNS AND SYMPTOMS ... 113

APPENDIX F: RESEARCH SPECIMEN COLLECTION/SHIPPING GUIDELINES ... 115

APPENDIX G: STUDY DRUG ORDER FORM ... 119

APPENDIX H: STRECK COLLECTION AND PROCESSING INSTRUCTIONS – FOR OUTSIDE OF DFCI LAB USE ONLY..... 120

1. OBJECTIVES

1.1 Study Design

This is a two-stage Phase 2 study assessing the efficacy of cabozantinib (alone or in combination with trastuzumab) in patients with metastatic breast cancer and brain metastases. Cabozantinib is a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGF receptor-2 (VEGFR2), RET, and KIT, when given as monotherapy. The population to be studied will consist of patients with metastatic breast cancer with measurable central nervous system (CNS) lesions. Treatment will consist of once daily oral dosing of cabozantinib (60 mg po day), during a 21 day cycle. Patients will also receive trastuzumab (8 mg/kg IV loading dose followed by 6 mg/kg IV every 3 weeks) if they have a HER2-positive breast cancer. Patients will undergo restaging scans at 6 weeks. Patients with stable or responsive disease after completion of 6 cycles may have the frequency of restaging scans reduced to once every 3 cycles. Patients with complete or partial responses, or stable disease, will continue to receive cabozantinib. Patients with progressive disease will be taken off study. Archival tissue from patients will be obtained if possible (please refer to Appendix F for archival tissue guidelines); however, if archival tissue is not available the patient may still participate in the study. The patient will have an opportunity to participate in an optional tumor biopsy study; however, the biopsy is not mandatory to participate in the study. Goal accrual is 37 patients (up to 40 patients will be enrolled), including 21 HER2-positive patients, 8 ER-positive patients, and 8 triple-negative patients.

1.2 Primary Objectives

1) To evaluate the CNS objective response rate (ORR), defined by RECIST 1.1, in patients with HER2-positive metastatic breast cancer and brain metastases

1.3 Secondary Objectives

1) To evaluate the CNS ORR in patients with hormone receptor positive metastatic breast cancer and brain metastases by RECIST 1.1

2) To evaluate the CNS ORR in patients with triple-negative metastatic breast cancer and brain metastases by RECIST 1.1

3) To evaluate the CNS ORR in patients with HER2-positive, hormone receptor positive, and triple-negative metastatic breast cancer and brain metastases by volumetric criteria and composite criteria

4) To evaluate ORR in non-CNS sites (by RECIST 1.1)

5) To evaluate Progression-Free Survival (PFS)

6) To evaluate the clinical benefit rate

7) To evaluate site of first progression (CNS versus non-CNS)

8) To evaluate overall survival (OS) in total study population.

9) To evaluate c-Met and phospho c-Met expression in archival tumor tissue

10) To evaluate the incidence of c-Met amplified circulating tumor cells at baseline

11) To evaluate potential plasma biomarkers of cabozantinib when given in combination with trastuzumab

12) To assess vascularity of CNS tumors, through descriptive analysis of tumor vessel size, cerebral blood volume, cerebral blood flow, perfusion, and diffusion before and after exposure to cabozantinib

13) To assess the safety and tolerability of cabozantinib when given in combination with trastuzumab

14) To collect blood to study cell-free DNA for comparison to tumor specimens

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 (see below).

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 of cabozantinib

2.3.1 Clinical Summary

The single agent maximum tolerated dose (MTD) on the once daily (qday) oral dosing schedule has been determined to be 60 mg po qday. Details of all studies may be found in the Investigator's Brochure.

2.3.2 Clinical Safety Profile

The adverse event (AE) and serious adverse event (SAE) data summarized in the following section includes those reported and entered in the clinical database and safety database published as of July 2013 (IBv9). The clinical studies with cabozantinib are ongoing, thus the AE data from the clinical database does not yet include all SAEs. Data from double-blinded studies are not presented. 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 February 28, 2013, 1311 subjects have been studied in open-label clinical trials with cabozantinib, including treatment with cabozantinib as a single agent. The available pooled data in this database include studies XL184-001, XL184-008, XL184-201, XL184-203, XL184-205, and XL184-301 cabozantinib arm. The most frequently (≥

20%) observed AEs, regardless of causality, were fatigue (66.7%), diarrhea (63.1%), decreased appetite (51.9%), nausea (51.9%), weight decreased (36.0%), PPES (35.9%), vomiting (34.1%), constipation (33.2%), dysgeusia (28.0%), hypertension (27.8%), dysphonia (26.3%), abdominal pain (23.3%), aspartate aminotransferase (AST) increased (23.0%), dyspnea (21.3%), headache (20.9%), rash (20.4%), and ALT increased (20.2%). The safety profile of single-agent cabozantinib is consistent across tumor types.

The most frequently (≥ 20%) observed AEs reported as related to cabozantinib, were fatigue (60.0%), diarrhea (56.1%), decreased appetite (44.1%), nausea (42.4%), PPES (35.6%), weight decreased (29.1%), dysgeusia (27.1%), hypertension (24.0%), vomiting (23.5%), dysphonia (22.0%), and AST increased (20.1%).

The most common AEs (≥ 5%) reported at severity of Grade 3 and above include fatigue (15.9%), diarrhea (11.1%), hypertension (9.7%), PPES (8.9%), lipase increased (6.8%), PE (5.9%), abdominal pain (5.5%), decreased appetite (5.3%), and asthenia (5.0%).

Serious Adverse Events

Out of all 1311 subjects enrolled in open-label, single-agent clinical trials with cabozantinib, 688 subjects (52.5%) experienced one or more SAEs recorded in the Argus Safety Database, and 300 (22.4%) subjects experienced one or more SAEs that were assessed to be related to treatment with cabozantinib. The most commonly reported SAEs (≥ 2%) were pulmonary embolism (5.1%), vomiting (3.4%), dehydration (3.2%), pneumonia (3.0%), nausea (3.0%), abdominal pain (2.4%), diarrhea (2.4%), deep vein thrombosis (DVT; 2.1%), and convulsion (2.0%). subjects), abdominal pain (in three subjects), and perirectal abscess (in three subjects). In addition, one late-breaking case of reversible posterior leukoencephalopathy syndrome (RPLS) was reported after the data cut-off in the double-blinded placebo-controlled Study XL184-301.

As of 28 February 2013, 192 fatal SAEs were reported (182 on single-agent cabozantinib or cabozantinib in combination with other therapies, 10 on placebo) across all open-label or unblinded company-sponsored studies (Studies evaluated include XL184-001, XL184- 002, XL184-008, XL184-014, XL184-201, XL184-202, XL184-203, XL184-205, XL184-209, XL184-900, and all clinical pharmacology studies, for a total N = 1754). The majority of these SAEs were attributed to disease progression (70.3%). Fifty-seven subjects had fatal SAEs that were not attributed to disease

progression, and of these 27 subjects had events related to cabozantinib (24 as single agent, 3 in combination with erlotinib).

Detailed information regarding the safety profile of Cabozantinib from all studies may be found in the Investigator's Brochure (version 9).

2.3.4 Clinical Pharmacokinetics

Pharmacokinetic (PK) analysis showed dose proportional increases in maximum plasma concentration (C_{max}) and area under the plasma concentration-vs-time curve (AUC) both for the powder-in-bottle (PIB) formulation (dose range: 0.08 to 11.52 mg/kg) and the capsule formulation (dose range: 125 mg to 175 mg). Terminal-phase half-life ($t_{1/2, z}$) values were 59.1 to 136 hours. More detailed information regarding cabozantinib PK from all studies and product metabolism in humans may be found in the Investigator's Brochure.

2.3.5 Blood Brain Barrier

No studies of cabozantinib exposure in cerebrospinal fluid in humans have been performed. Two preclinical studies evaluating tissue distribution of cabozantinib in brain or CNS tissue have been conducted. In a study employing nude mice dosed orally with 10 mg/kg cabozantinib, exposure in brain tissue was 1.32 ± 0.083 μM four hours post-dose, compared to 8.19 ± 0.709 μM in plasma at the same time point. A cabozantinib tissue distribution study in pigmented and albino rats has also been performed using radiolabeled cabozantinib. The exposure of CNS tissue to cabozantinib-associated radioactivity was relatively low (tissue to blood ratio of 0.09-0.10 μg equiv/g) compared to most other tissues (e.g. tissue to blood ratios of 2.65 μg equiv/g for liver, 1.28 μg equiv/g for lung, and 0.43 μg equiv/g for prostate gland).

2.3.6 Clinical Activity

In addition to MTC, cabozantinib has demonstrated findings consistent with broad clinical anti-tumor activity in early Phase 1 and Phase 2 studies in several other tumor types. In a randomized discontinuation trial (RDT) XL184-203, the following disease control rates (DCR = complete response [CR] + partial response [PR] + stable disease [SD]) at Week 12 were observed in tumor types including non-small cell lung cancer (NSCLC), 38%; breast cancer, 48%; melanoma, 46%; ovarian cancer, 53%; hepatocellular carcinoma (HCC), 66%; and CRPC, 66%. In Study XL184-008, clinical

activity was also observed in differentiated thyroid cancer (DTC; DCR = 73% at 24 weeks) and renal cell carcinoma (RCC; median progression-free survival [PFS] = 12.9 months). Observations of clinical activity have included decrease of soft tissue tumor lesions including visceral metastases, effects on metastatic lesions on bone scan (partial or complete bone scan resolution), reduction in serum markers of bone resorption and formation, reduction in circulating tumor cells (CTCs; subjects with prostate cancer), increases in hemoglobin, and improvements in bone pain and reductions in narcotic use in subjects with bone metastases. Activity in MTC and CRPC subjects is described in more detail below.

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

In the Phase 2 study XL184-203, cabozantinib demonstrated broad clinical activity in men with CRPC (Smith et al. 2013). During the RDT phase, the majority of CRPC subjects with bone metastases and elevated total alkaline phosphatase (t-ALP) levels at baseline showed reductions in t-ALP (Smith et al. 2013). Similarly, during the non-randomized expansion (NRE) phase, the majority of CRPC subjects at the 100 mg assigned dose showed reductions in circulating bone specific alkaline phosphatase (BSAP) (Smith et al. 2012). These effects were independent of prior or concomitant bisphosphonate treatment. Reductions in bone biomarkers were also evident in the 40 mg CRPC NRE cohort (de Bono et al, 2012). Effects on bone scan were assessed by an independent reader, and pain and narcotic use were prospectively assessed using an interactive voice recording system (IVRS) and a diary. Subjects achieved a bone scan

response (BSR) in both the 100 mg and 40 mg assigned NRE dose cohorts (67% and 49%, respectively). Among subjects with baseline pain of at least 4 (0-10 scale by Brief Pain Inventory [BPI]), a majority had at least a decrease of 30% in the average daily worst pain compared with baseline in both cohorts (100 mg: 64% of subjects; 40 mg: 69% of subjects). In addition, more than half of subjects decreased narcotic use.

Table 2. Summary of Clinical Studies of Cabozantinib in Cancer Patients

Protocol Number	Study Population	Study Title	Study Status
Phase 1			
XL184-001	Advanced tumors, MTC	A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of XL184 Administered Orally to Subjects with Advanced Malignancies	Complete
XL184-002	GB	A Phase 1 Dose Finding Study of the Safety and Pharmacokinetics of XL184 Administered Orally in Combination with Temozolomide and Radiation Therapy in the First Line Treatment of Subjects with Glioblastoma	Complete – analysis pending
XL184-008	Solid tumors, RCC, DTC	A Phase 1 Drug-Drug Interaction Study of the Effects of XL184 on the Pharmacokinetics of a Single Oral Dose of Rosiglitazone in Subjects with Solid Tumors	Complete – analysis pending
XL184-014	Solid tumors	Phase 1 Multiple Ascending Dose Study of XL184 Monotherapy in Japanese Subjects with Advanced or Metastatic Solid Tumors	Active, enrollment ongoing
Phase 1/2			
XL184-202	NSCLC	A Phase 1b/2 Study of XL184 with or without Erlotinib in Subjects with Non-Small Cell Lung Cancer	Complete
Phase 2			
XL184-201	GB	A Phase 2 Study of XL184 in Subjects with Progressive or Recurrent Glioblastoma Multiforme in First or Second Relapse	Complete – analysis pending
XL184-203	CRPC, ovarian, NSCLC, HCC, melanoma, breast, gastric/GEJ, SCLC, pancreatic	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	Active, enrollment completed
XL184-205	GB	A Phase 2 Non-Comparative Randomized Open-Label Study of Multiple Regimens of Single-Agent XL184 in Subjects with Grade IV Astrocytic Tumors in First or Second Relapse	Complete – analysis pending
XL184-301	MTC	An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 Versus Placebo in Subjects with Unresectable, Locally Advanced or Metastatic Medullary Thyroid Cancer (EXAM)	Active, enrollment completed

XL184-307	CRPC	A Phase 3, Randomized, Double-Blind, Controlled Study of Cabozantinib (XL184) vs. Prednisone in Metastatic Castration-Resistant Prostate Cancer Patients who have Received Prior Docetaxel and Prior Abiraterone or Enzalutamide [COMET-1]	Active, enrollment ongoing
XL184-306	CRPC	A Phase 3, Randomized, Double-Blind, Controlled Trial of Cabozantinib (XL184) vs. Mitoxantrone Plus Prednisone in Men with Previously Treated Symptomatic Castration-Resistant Prostate Cancer [COMET-2]	Active, enrollment ongoing
Maintenance "Roll Over" Study			
XL184-900	Advanced malignancies	A Maintenance Study Evaluating the Long Term Safety of XL184 in Subjects with Advanced Malignancies Previously Enrolled in Other XL184 Studies	Active, enrollment ongoing
Expanded Access Study			
XL184-209	MTC	An Open-Label, Expanded Access Study of Cabozantinib (XL184) in Subjects with Unresectable, Locally Advanced, or Metastatic Medullary Thyroid Cancer	Active, enrollment completed

2.4 Trastuzumab

2.4.1 Overview

Trastuzumab is a humanized anti-HER2 antibody that binds to the subdomain IV of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2 cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand-independent, HER2-mediated mitogenic signaling.

2.4.2 Safety profile

Trastuzumab is a humanized murine antibody. It was engineered so that conserved units of the antibody molecule were transcribed from human DNA sequences, while the specific anti-HER2 domain remained of mouse DNA origin. As a result of these modifications, the antibody is not immunogenic in the vast majority of people. The resulting antibody (Herceptin®, Trastuzumab; Genentech) has been studied both as a single agent and in combination therapy for metastatic breast cancer.

Trastuzumab is associated with the potential for left ventricular cardiac dysfunction and congestive heart failure (CHF). In the pivotal trial of trastuzumab for metastatic breast cancer, the rate of cardiac dysfunction was highest when given concurrently with doxorubicin, with a rate of NYHA class III/IV CHF of 4% in patients receiving

trastuzumab with paclitaxel (D. Slamon & Leyland-Jones, 2001). In an adjuvant study of carboplatin, docetaxel, and trastuzumab (BCIRG 006), the rate of grade 3 or 4 left ventricular cardiac dysfunction was 0.3% and no cardiac deaths were observed (D. Slamon, Eiermann, Robert, & Al., 2006).

Other reported adverse events include infusion reactions, characterized by fever, chills, nausea, vomiting, headache, dyspnea, hypotension, and rash. Trastuzumab may also exacerbate chemotherapy-induced neutropenia. Very rarely, trastuzumab can result in serious and fatal pulmonary toxicity.

2.4.3 Rationale for Trastuzumab in HER2-positive Breast Cancer

The HER2/*neu* oncogene lies on chromosome 17q, and encodes a transmembrane glycoprotein (p185) with homology to the epidermal growth factor receptor. Overexpression of HER2 at the genetic or protein level is observed in 20 to 25% of all breast cancers, and is primarily a consequence of gene amplification (D. J. Slamon et al., 1987, 1989).

Trastuzumab has been studied as first-line therapy for metastatic breast cancer. In a study of 114 women with HER2-positive tumors who had not previously received chemotherapy for advanced breast cancer, a response rate of 26% was observed with single agent trastuzumab (Vogel, 2002). Trastuzumab has also been used in combination with other chemotherapy to treat women with metastatic breast cancer. In a phase III clinical trial, patients with HER2-positive metastatic breast cancer were randomized to receive treatment with either chemotherapy, or chemotherapy and trastuzumab given concurrently (Slamon et al., 2001). A subsequent analysis of this phase III study has demonstrated that initial therapy with trastuzumab and chemotherapy, as opposed to chemotherapy alone, is associated with both higher response rates, as well as improved time-to-progression and, most significantly, improved overall survival.

In patients who have progressed on trastuzumab, data from one study supports the concept that continuation of trastuzumab beyond progression improves the efficacy of chemotherapy on systemic (i.e. extra-CNS) metastases. In a study of 156 patients who had previously progressed on trastuzumab-based therapy, the continuation of trastuzumab with capecitabine was associated with a doubling of the response rate and improvement in PFS compared to capecitabine alone (Von Minckwitz, Vogel, Schmidt, & Al., 2007).

Trastuzumab does not cross the blood-brain barrier (Pestalozzi & Brignoli, 2000) and no CNS responses to trastuzumab, given intravenously, have been documented in the literature. The rationale for including trastuzumab is to maintain maximum disease control systematically (i.e. outside of the CNS). It is anticipated that the addition of trastuzumab to patients with HER2-positive breast cancer will not alter the primary endpoint of CNS objective response.

2.5 Brain Metastases in Breast Cancer

It is estimated that approximately 10-15% of women with metastatic breast cancer will eventually develop brain metastases (Tsukada, Fouad, Pickren, & Lane, 1983; Tsukada, Hurwitz, Kashi, & Al., 1983). It has been noted that several features predict an increased risk of CNS recurrence, including young age, African American ethnicity, HER2 positive or ER-negative primary breast cancer, and the presence of visceral metastases (Barnholtz-Sloan et al., 2004). Our group and Dana-Farber was the first to describe an increased incidence in women with HER2-positive metastatic breast cancer, of whom up to one-third will be diagnosed with brain metastases (Lin, Bellon, & Winer, 2004). More recently, a high rate of brain metastases has also been described in patients with triple-negative (ER, PR, and HER2-negative) tumors with an incidence of 46% (Lin et al., 2008). Brain metastases are associated with considerable morbidity and mortality.

2.6 Rationale

Few treatments exist for such brain metastases from breast cancer. Treatment is mainly aimed at palliation, and generally includes whole brain radiation (WBRT), stereotactic radiosurgery (SRS), and/or surgical resection. As systemic therapies have improved, CNS progression after WBRT and/or SRS is becoming a significant problem. Currently there is no optimal therapy once this occurs. Unfortunately, very few prospective studies have examined the role of chemotherapy in the treatment of brain metastases from breast cancer, and most studies of novel agents have excluded patients with brain metastases. Developing effective agents for the treatment of brain metastases from breast cancer is critical.

Recently, data suggests that anti-angiogenic therapy can be given safely to patients with brain metastases, and that clinical activity has been demonstrated. Norden and colleagues reported a retrospective case series of 55 patients treated with bevacizumab and chemotherapy in patients with glioma (Norden et al., 2008). Of these patients, 2.3%

achieved a complete response, 31.8% partial response, 29.5% minimal response, and 29.5% stable disease. Vredenburgh and colleagues treated a total of 35 patients with recurrent glioma with irinotecan and bevacizumab and demonstrated a 57% ORR. Given the postulated importance of the VEGF pathway in the pathogenesis of brain metastases from breast cancer, exploration of anti-angiogenesis approaches for CNS metastases from breast cancer is warranted. Nancy Lin and colleagues have conducted a trial of carboplatin + bevacizumab +/- trastuzumab for patient with metastatic breast cancer and brain metastases and demonstrated a composite CNS ORR of 63% (Lin et al, 2013).

A pre-clinical study in mice by Kodack and colleagues found that treating HER2-amplified breast cancer patients with a combination of trastuzumab and anti-VEGF receptor-2 (VEGFR2) antibody slowed tumor growth in the brain and conferred a significant survival benefit. This benefit was postulated to be due to enhanced antiangiogenic effects of these two drugs reducing total and functional microvascular density in the brain, resulting in more necrosis of brain lesions (Kodack et al., 2012). Taken together, these evidence suggest some clinical efficacy of anti-angiogenic therapy in treating brain tumors and metastases that warrant further clinical study.

Evidence shows that inhibiting VEGF alone may only produce a temporary clinical response, but that simultaneously inhibiting both VEGF and MET with cabozantinib can achieve a more durable clinical benefit. Though VEGF inhibitors alone are therapeutically effective for many types of cancer, their clinical benefit often only last for several weeks or months before tumor progression recurs. Preclinical studies have found that VEGF pathway inhibition initially slows tumor growth and reduces tumor vasculature, this is followed by a refractory period of rapid revascularization and increased tumor invasiveness (Casanovas, Hicklin, Bergers, & Hanahan, 2005; Ebos et al., 2009). Resistance to VEGF pathway inhibition may develop in response to hypoxia. Under hypoxic conditions, hypoxia-inducible factor 1α is upregulated, which in turn increases expression of both VEGF and MET (Kitajima, Ide, Ohtsuka, & Miyazaki, 2008; Pennacchietti et al., 2003). These responses are a compensatory mechanism during periods of hypoxia, and result in more angiogenesis or migration away from the hypoxic zone. Because VEGF pathway inhibition can result in hypoxia, it may also subsequently trigger MET expression. Several studies have shown that the MET pathway plays an important role in development of resistance to VEGF pathway inhibition by sunitinib treatment (Pàez-Ribes et al., 2009; Shojaei et al., 2010).

Moreover, additional evidence demonstrates that VEGF inhibitors such as cediranib can lead to increased tumor invasiveness and metastasis and higher MET expression levels (di Tomaso et al., 2011). Taken together, this suggests that simultaneously targeting both MET and VEGF can critically disrupt angiogenesis, tumorigenesis and cancer progression.

Evidence from studies suggests that cabozantinib has anti-angiogenic (anti-VEGFR2) activity, CNS penetration, and activity in breast cancer, and could be efficacious in treatment of brain metastases from breast cancer. Cabozantinib inhibits c-met, RET, VEGFR2/KDR, and KIT. The safety and tolerability of cabozantinib have been established in a Phase I, single-arm, dose-escalation studies in adult patients with advanced solid tumors, and in another Phase Ib trial evaluating the combination of cabozantinib and erlotinib. The most commonly reported drug-related adverse events were diarrhea (40%), fatigue (37%), anorexia (31%), nausea (29%), PPE syndrome (20%), increased AST (19%), and rash (18%). Data from a randomized discontinuation study in heavily pretreated patients with metastatic breast cancer demonstrated an ORR of 14% and a clinical benefit rate at 12 weeks of 48%. Additionally, there are two ongoing studies of cabozantinib in metastatic breast cancer, one in ER+ disease, and one in triple-negative breast cancer. We have noted two patients who likely had brain metastases at time of enrollment onto study, though it was unknown at the time, and noted that there was treatment effect in the brain with cabozantinib. One of these patients had TNBC, and another had ER+, HER2- breast cancer.

The c-Met receptor is the only high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor. Binding of HGF to the c-Met extracellular ligand-binding domain results in receptor multimerization and phosphorylation of multiple tyrosine kinase residues in the intracellular portion of c-Met. Activation of c-Met results in the binding and phosphorylation of adaptor proteins, such as Gab-1, Grb-2, Shc, and c-Cbl, and subsequent activation of signal transducers such as PI3K, STATs, ERK1 and 2, and FAK (Christensen et al., 2003; Trusolino, Bertotti, & Comoglio, 2001). c-Met and HGF are expressed in numerous tissues, and their expression is predominantly confined to cells of epithelial and mesenchymal origin, respectively (Trusolino et al., 2001). HGF and Met promote cell proliferation, motility, invasion, and stimulate tissue repair and tumor growth (Bottaro et al., 1991; Gherardi & Stoker, 1990; Ma, Maulik, Christensen, & Salgia, 2003; Nakamura et al., 1989; Stoker, Gherardi, Marion, & Gray, 1987). c-Met overexpression, with or without gene amplification, has been reported in a variety of

malignancies, including breast, colorectal, lung, gastric, and hepatocellular carcinoma (Boix et al., 1994; Kuniyasu, Yasui, Yokozaki, Kitadai, & Tahara, 1993). Elevated expression of c-Met has been associated with poor prognosis in breast cancer (Kang et al., 2003; Lengyel et al., 2005). Interestingly, data suggests the HGF and c-Met are expressed to a greater degree in triple-negative and HER2-positive breast cancer (Camp, Rimm, & Rimm, 1999; Sheen-Chen, Liu, Eng, & Al, 2005; Toi et al., 1998; Yamashita et al., 1994).

Mouse models also suggest a critical role of the c-Met pathway during the development of triple-negative breast cancer. Mice harboring mutant c-Met knock-in or mutant c-Met transgene under mouse mammary tumor virus promoter, developed breast cancers with a triple-negative phenotype (Graveel, DeGroot, Su, & Al, 2009; Ponzo, Lesurf, Petkiewicz, & Al, 2009). Additionally, a c-Met-driven pathway signature clustered with basal and triple-negative breast cancer from human tissue samples and correlated with worse patient outcome (Graveel et al., 2009; Ponzo et al., 2009). These studies suggest that c-Met expression and activation is important for initiation and progression of triple-negative breast cancer.

C-Met has been found to frequently be coexpressed in HER2+ breast cancer and appears to contribute to resistance through sustained AKT activation. Resistance to trastuzumab presents a significant barrier to effective treatment of HER2+ breast cancer. Loss of Met function, either through RNA interference-mediate depletion or small molecular mediated inhibition, significantly improves the response to trastuzumab (Shattuck, Miller, & Carraway, 2008). Conversely, Met activation protects the cells against trastuzumab. The mechanism of resistance likely lies in the ability of Met to drive EGFR-independent/ERbB3-dependent PI3K/AKT activation.

In ER-positive breast cancer cells, activation of the receptor tyrosine kinase by its ligand results in increased ER phosphorylation on Ser118 and Ser167 and estrogen-independent activation of ER transcriptional activity (Plaza-Menacho, Morandi, Robertson, & Al, 2010). Expression of RET protein is significantly associated with ER positive tumors and with the development of recurrent disease after adjuvant tamoxifen treatment, thus along with MET, cotargeting RET may be a potentially important therapeutic target in ER-positive and hormone-resistant breast cancers.

Given the data suggesting the c-Met expression is increased in the triple-negative breast cancer, may be important in trastuzumab-resistant HER2+ breast cancer, and RET

inhibition may be important in hormone refractory ER+ breast cancer, cabozantinib may have benefit in all subtypes of breast cancer. Moreover, data suggests that cabozantinib penetrates the blood brain barrier, and with its anti-angiogenic activity, may be critical for treatment of brain metastases. We will assess the efficacy of cabozantinib in patients with metastatic breast cancer with known brain metastases. Patients with HER2+ breast cancer will receive trastuzumab in combination with cabozantinib.

2.7 Correlative Studies Background

2.7.1 Evaluate c-Met and phospho-c-Met expression in FFPE tumor tissue

Since cabozantinib inhibits MET expression, it is hypothesized that tumors in patients who express higher levels of c-Met will respond more robustly to cabozantinib therapy. Testing c-Met and phospho-c-Met expression in previously collected FFPE tumor tissue is one method to genotype patient tumors. Caveats to this technique are that patients' malignant cells may have acquired additional mutations since these tissues were collected, and this sampling may not detect the heterogeneity of gene expression within a tumor. However, this technique is an accessible option to profile genetic expression, especially when paired with additional profiling approaches. In this study, patients will be dichotomized as to whether or not their tumor expresses c-Met and the association between expression and response to cabozantinib will be explored.

2.7.2 Evaluate the incidence of c-Met amplification in circulating tumor cells at baseline

Simultaneously, we will also use another approach to determine c-Met amplification levels based on circulating tumor cells. These results may corroborate the c-Met and phospho-c-Met expression studies with FFPE tumor tissue samples. The primary advantage of this technique is that malignant cells are collected via purification of circulating tumor cells (CTCs) from whole blood, which is a far less invasive technique for malignant cell sampling than traditional biopsies. Interestingly, these CTCs are indicative of tumor metastases and predictive of clinical outcomes in breast cancer patients (Cristofanilli et al., 2004). Patients will be grouped as to whether or not their tumor has amplified c-Met and the association between amplification and response to cabozantinib will be evaluated.

2.7.3 Evaluate potential plasma biomarkers of cabozantinib

Exploratory analyses of potential biomarkers of cabozantinib activity will be performed by measuring proteins in the plasma and circulating cells at baseline, on days 1 and 8 of each cycle of therapy, and, if available, at the end of treatment. Plasma analysis will be carried out for a panel of circulating angiogenic and inflammatory molecules previously identified as potential biomarkers of response to anti-VEGF therapy in breast cancer patients (Boucher et al., ASCO 2013). They include vascular endothelial growth factor (VEGF), placental-derived growth factor (PlGF), soluble (s)VEGFR1, basic fibroblast growth factor (bFGF), and stromal-derived factor 1α (SDF1α). In addition, we will measure the plasma concentration of biomarkers that are related to cabozantinib activity: HGF, s-MET, s-c-KIT and sVEGFR2. Finally, we will evaluate biomarkers of tumor hypoxia, by measuring plasma carbonic anhydrase IX **(**CAIX) levels as well as biomarkers of osteoclast and osteoblast activity (plasma C-telopeptide and total alkaline phosphatase). Baseline and on treatment biomarker values will be correlated with patient's response to cabozantinib therapy.

2.7.4 Vessel density and tortuosity

Visualization of vessel density and tortuosity enables longitudinal assessment of cabozantinib's impact on tumor angiogenesis within brain tumors.

The feasibility of this technique has been previously demonstrated in a prospective trial of lapatinib for patients with brain metastases from HER2-positive breast cancer (Bullitt et al., 2007). This study demonstrated widespread abnormalities in vessel shape in the brain at baseline, in some cases extending far beyond the visible tumors. Vessel tortuosity measurements enabled correct prediction of treatment failure earlier than other methods. In that small study, of the three patients who had quantitative improvements in vessel tortuosity at 2-month follow-up, each of the two patients for whom further follow up data were available remained on protocol-based therapy for 6 months or longer. Particularly given the postulated mechanism of action of cabozantinib, visualization of changes in vessel tortuosity is of great interest.

2.7.5 Cerebral blood volume, blood flow, and vessel size

Vascularity of tumors indicates active angiogenesis, a process that cabozantinib targets through its inhibitory effects on VEGFR and c-MET. Patients on this study will receive routine brain MRIs to assess the vascularity of their brain tumors – blood flow, blood volume, permeability and surface area of capillary bed. In a previous study of AZD2171,

a small molecule inhibitor of VEGFRs, these techniques successfully demonstrated normalization of tumor vessels and reduction of vasogenic edema in patients with gliomas. Furthermore, early changes in vascular parameters were predictive of improved overall outcomes in these patients (Batchelor TT et al., 2007).

2.7.6 Blood sample collection

Blood will be collected at baseline and at the end of treatment for cell-free DNA (cfDNA). The cfDNA will be processed by the Clinical Trial Core Laboratory at DFCI and then banked in the DF/HCC Clinical Trials Core laboratory for future research purposes. The banked samples will be used to analyze DNA, RNA and protein in future studies.

3 PARTICIPANT SELECTION

3.1 Inclusion Criteria

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

3.1.1 Patients must have histologically or cytologically confirmed invasive breast cancer, with stage IV disease. Patients without pathologic or cytologic confirmation of metastatic disease should have unequivocal evidence of metastasis from physical examination or radiologic evaluation.

(i) Measurable disease: patients must have measurable CNS disease, defined as at least one parenchymal brain lesion that can be accurately measured in at least one dimension with the longest diameter ≥10 mm by local radiology review (measurable non-CNS disease is not required for study participation)

(ii) Patients will be defined as HER2+ if either the primary tumor and/or the metastasis are HER2-positive, defined as 3+ by IHC or FISH≥2.0

3.1.2 New or progressive CNS lesions, as assessed by the patient's treating physician.

(i) It is anticipated that some patients may have multiple progressive CNS lesions, one or several of which are treated with SRS or surgery with residual untreated lesions remaining. Such patients are eligible for enrollment on this study providing that at least one lesion is measurable

(≥10 mm) per RECIST 1.1. The location of the measurable lesion should be documented in the patient chart and case report form.

(ii) Patients who have had prior cranial surgery are eligible provided that there is evidence of measurable residual or progressive lesions, and at least 3 months have passed since surgery. If a patient has surgical resection followed by WBRT, then there must be evidence of progressive CNS disease after the completion of WBRT

(iii) Patients who had had prior WBRT and/or SRS and then whose lesions have progressed thereafter are also eligible. In this case, lesions that have been treated with SRS may be considered as target lesions if there is unequivocal evidence, in the opinion of the treating physician, of progression.

(iv) Patient who have not previously been treated with cranial radiation (e.g. WBRT or SRS) are eligible to enter the study, but such patients must be asymptomatic or minimally symptomatic from their CNS metastases and not requiring corticosteroids.

3.1.3 For patients who have received prior cranial radiation, no increase in corticosteroid dose in the week prior to the baseline brain MRI

3.1.4 Prior therapy: Patients must have discontinued all chemotherapy, investigational therapy or biologic therapy at least 14 days prior to initiating study treatment (with the exception of trastuzumab for patients with HER2+ breast cancer)

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

3.1.6 Cohort 1: HER2-positive, defined by ASCO CAP 2013 guidelines:

- IHC 3+ based on circumferential membrane staining that is complete, intense

-OR-

- FISH positive based on one of the three following criteria:

- Single-probe average HER2 copy number ≥ 6.0 signals/cell; **OR**
- Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 6.0 signals/cell; **OR**
- Dual-probe HER2/CEP17 ratio ≥ 2.0

Cohort 2: Hormone receptor positive (ER-positive and/or PR-positive, defined as ≥ 1% staining by immunohistochemistry) and HER2-negative

Cohort 3: Triple negative (ER-negative, PR-negative, HER2-negative)

3.1.7 The subject is ≥18 years old on the day of consent

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

3.1.9 Patients must have normal organ and marrow function and laboratory values as follows within 14 days before the first dose of cabozantinib:

(i) Absolute neutrophil count ≥ 1000/mm^3 without colony stimulating factor support

(ii) Platelets ≥ 100,000/mm^3

(iii) Hemoglobin ≥ 9 g/dL

(iv) Total Bilirubin ≤ 1.5 mg/dL × the ULN

(v) Serum albumin ≥ 2.8 g/dl

(vi) 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;

(vii) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × the ULN. For patients with documented liver metastases, AST/ALT ≤ 5.0 times the upper limit of normal.

(viii) Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis

(ix) Urine protein:creatinine ratio ≤ 1

(x) Serum phosphorus, calcium, magnesium and potassium ≥ LLN

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

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

3.1.12 Female subjects of childbearing potential must not be pregnant 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, low body weight, ovarian suppression or other reasons.

3.1.13 Patients on bisphosphonates may continue receiving bisphosphonate therapy during study. Patients wanting to initiate bisphosphonate therapy may do so.

3.1.14 The subject has had an assessment of all known non-CNS disease sites eg, by computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone scan as appropriate, within 28 days before the first dose of cabozantinib

3.1.15 Research MRI sequences performed at Massachusetts General Hospital Charlestown Navy Yard must be completed ≤ 7 days of Cycle 1 Day 1

3.1.16 Clinical MRIs performed at baseline must be completed within 28 days of the first dose of cabozantinib

3.2 Exclusion Criteria

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

3.2.1 The subject has received cabozantinib or another c-Met inhibitor (please note ARQ 197 is not considered a MET inhibitor for purposes of this study given data to suggest it inhibits tubulin)

3.2.2 The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders including:

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

ii. Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of cabozantinib;

iii. Any history of congenital long QT syndrome;

iv. Any of the following within 6 months before the first dose of cabozantinib: unstable angina pectoris; clinically-significant cardiac arrhythmias; stroke (including transient ischemic attack (TIA), or other ischemic event); myocardial infarction; thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (eg, vena cava filter) are not eligible for this study).

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

i. Any of the following within 28 days before the first dose of cabozantinib: intra-abdominal tumor/metastases invading GI mucosa; patients must be completely recovered from any evidence of active peptic ulcer disease; patients must be completely recovered from these conditions - any evidence or inflammatory bowel disease (including ulcerative colitis

and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis; malabsorption syndrome.

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

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

d. Other clinically significant disorders such as:

i. active infection requiring systemic treatment within 28 days before the first dose of cabozantinib;
ii. serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of cabozantinib;
iii. history of organ transplant;
iv. concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of cabozantinib.

3.2.3 Leptomeningeal disease as the only site of CNS involvement

3.2.4 Known contraindication to MRI with gadolinium contrast, such as cardiac pacemaker, shrapnel, or ocular foreign body

3.2.5 More than 2 seizures over the last 4 weeks prior to study entry

3.2.6 Grade 1 or higher CNS hemorrhage on baseline brain MRI, or history of grade 2 or higher CNS hemorrhage within 12 months

3.2.7 The subject has experienced any of the following:

a. clinically-significant GI bleeding within 6 months before the first dose of cabozantinib;

b. hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of cabozantinib;

c. any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of cabozantinib.

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

3.2.9 The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib

3.2.10 The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic LMWH are permitted;

3.2.11 The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of cabozantinib.

3.2.12 Inability to swallow intact tablets

3.2.13 Pregnant or lactating females

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

3.2.15 Radiation therapy within 7 days before the first dose of cabozantinib. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible

3.2.16 The subject is known to be positive for the human immunodeficiency virus (HIV)

3.2.17 Major surgery within 12 weeks before the first dose of cabozantinib. Complete wound healing from major surgery must have occurred 1 month before the first dose of cabozantinib. Minor surgery (including uncomplicated tooth extractions) is allowed if it occurred 28 days before the first dose of cabozantinib with complete wound healing at least 10 days before the first dose of cabozantinib. Subjects with clinically relevant ongoing complications from prior surgery are not eligible

3.2.18 QTcF > 500 msec on average of screening EKGs performed within 28 days of first dose of cabozantinib. Three EKGs must be performed at screening. If the average of these three consecutive results for QTcF is > 500 msec, the subject is ineligible.

3.2.19 Active infection requiring IV antibiotics at Day 1 of cycle 1

3.2.20 No prior lapatinib within 7 days prior to initiation of protocol treatment

3.2.21 Patients may not receive any concurrent investigational agents while on study

3.2.22 Patients may not receive any cancer-directed concurrent therapy, such as concurrent chemotherapy, radiotherapy, or hormonal therapy while on study.

3.2.23 Previously identified allergy or hypersensitivity to components of the cabozantinib formulations

3.2.24 The subject requires chronic concomitant treatment with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort).

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Both men and women of all races and ethnic groups are eligible for this trial.

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.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration for DF/HCC 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:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

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

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

5 TREATMENT PLAN

5.1 Treatment Overview

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.

The target accrual is up to a maximum of 40 patients who receive at least one dose of protocol-based therapy in order to enter 37 patients who have "assessable" CNS disease. Assessable disease is defined as at least one parenchymal brain lesion that can be accurately measured in at least one dimension with the longest dimension ≥ 10 mm by local radiology review (measureable non-CNS disease is not required for study participation). The estimated rate of accrual is 1-2 patients per month. Patients will be followed for up to two years after removal from study or until death, whichever comes first.

Exelixis will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 60-mg, and 20-mg yellow film-coated tablets. The 60-mg tablets are oval, and the 20-mg tablets are round.

Subjects will receive cabozantinib orally administered daily and continuously. Dosing will begin at 60 mg cabozantinib per day taken orally for all patients with dosing delays/dose modifications as outlined in Section 6.

A full cycle length will be defined as 21 days (3 weeks). Cabozantinib will be given on day 1 and taken daily for 21 day cycle. Patients with HER2 positive disease will concurrently receive 6 mg/kg intravenous trastuzumab on Day 1 of each cycle. HER2 positive patients naïve to trastuzumab receive an 8 mg/kg loading dose during cycle 1, and resume the 6 mg/kg dosing for every subsequent cycle. Correlative imaging studies

will be done 21 days post dose of cabozantinib at the Cycle 2 Day 1 timepoint (day 22), prior to patient receiving Cycle 2 Day 1 dose.

Cycle 2 of treatment will begin 21 days following the first dose of cabozantinib. Starting with cycle 2, minor deviations to the treatment schedule are allowed for patient scheduling requests with a $\pm$ 4 days window (i.e. infusion chair availability, weather-related issues, vacation, etc.). Additionally, minor deviations to the scan schedule will be allowed (i.e. Day 22 brain MRI, CT, MUGA) for patient scheduling requests with a $\pm$ 7 days window.

Subjects will be provided with a sufficient supply of cabozantinib and instructions for taking the cabozantinib on days without scheduled clinic visits. After fasting (with exception of water) for 2 hours, participants will take cabozantinib 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 cabozantinib. Participants should be instructed to swallow the tablets whole and not crush, chew or dissolve in water prior to swallowing. Participants should record dosing time and doses taken in a study drug dosing diary while on cabozantinib. 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. As described in Appendix D, Participant's Medication Diary, if it has been more than 12 hours since missing their scheduled dose, then the participants should not take the missed dose. However, if it has been less than 12 hours since the missed dose, then the dose should be taken immediately and the participant should continue taking their dose at the regular time the next day. Participants must be instructed to not make up missed doses that are vomited. Participants should be instructed to wait until the next day to take the next scheduled dose and should be reminded to tell their doctor or nurse at their next visit which dose(s) were missed.

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

Table 3. Cycle 1 and beyond

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Cabozantinib	60 po qday	Oral	Daily	3 weeks (21 days)
Trastuzumab*	6 mg/kg (8mg/kg loading dose)	IV	Day 1	

*Trastuzumab will only be administered to patients with HER2-positive disease. Loading dose of trastuzumab not required if patients have received a weekly trastuzumab dose (2 mg/kg) within 3 weeks of anticipated trastuzumab start date on this protocol, or if patients have received a Q3 weekly dose (6 mg/kg) of trastuzumab within 6 weeks of anticipated trastuzumab start date on this protocol. In such cases, patients should receive 6 mg/kg IV starting on Cycle 1 Day 1.

5.2 Pre-treatment Criteria

The following pre-treatment criteria must be met in order to begin cabozantinib on **Cycle 1, Day 1**:

- Absolute neutrophil count (ANC) $\geq 1000/mm^3$
- Platelets $\geq 100{,}000/mm^3$
- Total bilirubin $\leq 1.5 \times$ the upper limit of normal
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3\times$ the upper limit of normal for patients with no liver involvement; or $\leq 5 \times$ the upper limit of normal for patients with liver involvement

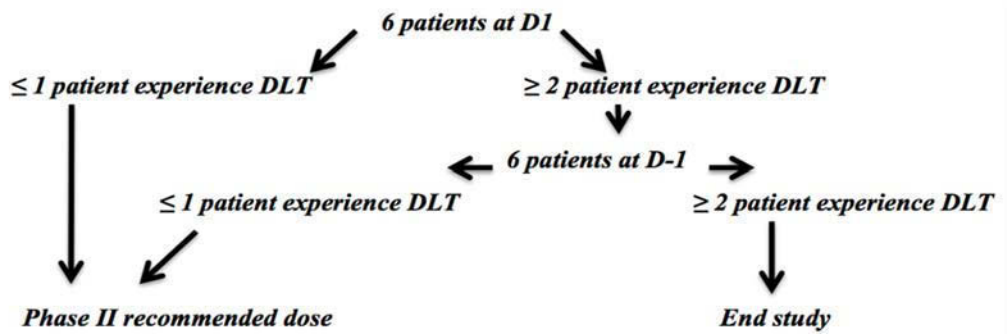
- Urine protein/creatinine ratio (UPCR) ≤ 1.

The following pre-treatment criteria must be met in order to begin cabozantinib on **Day 1 of each subsequent cycle**:

- Absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelets ≥ 100,000/mm^3
- Total bilirubin ≤ 1.5 × the upper limit of normal
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × the upper limit of normal if no liver involvement; or ≤ 5 × the upper limit of normal for patients with ≤ 3 × the upper limit of normal (i.e. Grade 1) LFTs at baseline or liver involvement
- Urine protein/creatinine ratio (UPCR) ≤ 1.

5.3 Initial Safety Evaluation of cabozantinib + trastuzumab

As an extra safety precaution, accrual will be paused when 6 patients have received first doses of cabozantinib and trastuzumab in this cohort. These 6 patients will be observed for 3 weeks and assessed for DLTs (dose-limiting toxicities), 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 to the combination of cabozantinib and trastuzumab, if, in the opinion of the principal investigator, any such SAE warrants further evaluation or discontinuation of the cohort. If DLTs are observed in 1 or fewer patients, accrual will continue at a starting cabozantinib dosage of 60 mg po qday. If 2 or more patients experience a DLT, cabozantinib dosage will be reduced to 40 mg po qday, and an additional DLT safety assessment will be done after enrollment of another 6 patients. If DLTs are observed in 1 or fewer patients, accrual will continue at a starting cabozantinib dosage of 40 mg po qday. If 2 or more patients experience a DLT, accrual to the HER2-positive cohort will be stopped permanently. Management for these patients is illustrated below.



	Cabozantinib dose	**Trastuzumab dose**
Dose Level 1 (D1)	60 mg po qday	6 mg/kg IV (every 3 weeks)
Dose Level -1 (D-1)	40 mg po qday	6 mg/kg IV (every 3 weeks)

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 3 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 6 patients in the trastuzumab/cabozantinib pilot cohort:

1. Any AE that results in a dose reduction during the DLT evaluation period
2. Non-Hematologic Toxicity

    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 hypertension controlled with medical management

j. Grade 3 hepatic transaminase (ALT or AST) lasting less than 72 hours

Note: For patients with Grade 1 hepatic transaminase at baseline as a result of liver or bone metastases, a ≥ 1.5 fold increase in AST or ALT, or hepatic transaminase ≥ 5 x the upper limit of normal (ULN) lasting more than 72 hours will be considered a DLT. For patients with grade 2 hepatic tranasminases at baseline as a result of liver or bone metastases, hepatic transaminase >7.5x ULN lasting more than 72 hours will be considered a DLT.

3. Hematologic Toxicity

a. Grade 3 neutropenia with infection requiring intervention or lasting > 7 days, or Grade 4 neutropenia

b. Grade 3 or 4 febrile neutropenia

c. Grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding

d. Other Grade 4 hematologic toxicities (e.g., anemia)

4. Failure to take more than 7 days of treatment within Cycle 1 due to treatment-related adverse effects

5. Any cabozantinib-related death

5.4 Agent Administration

5.4.1 Cabozantinib

Subjects will receive cabozantinib orally administered daily and continuously. Dosing will begin at 60 mg cabozantinib per day taken orally for all patients with dosing delays/dose modifications as outlined in Section 6.

Participants will be provided with a sufficient supply of cabozantinib and instructions for taking the cabozantinib on days without scheduled visits. After fasting (with exception of water) for 2 hours, participants will take cabozantinib 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 cabozantinib. Participants should be instructed to swallow the tablets whole and not chew them prior to swallowing. Participants should record dosing time

and doses taken in a study drug dosing diary while on cabozantinib. 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. As described in Appendix D, Participant's Medication Diary, if it has been more than 12 hours since missing their scheduled dose, then the participants should not take the missed dose. However, if it has been less than 12 hours since the missed dose, then the dose should be taken immediately and the participant should continue taking their dose at the regular time the next day. Participants must be instructed to not make up missed doses that are vomited. Participants should be instructed to wait until the next day to take the next scheduled dose and should be reminded to tell their doctor or nurse at their next visit which dose(s) were missed.

5.4.2 Trastuzumab

For HER2-positive patients, trastuzumab is administered intravenously in the outpatient setting. The dose for initial treatment with trastuzumab is 8 mg/kg IV unless the patient has received qweek dose (2mg/kg) trastuzumab ≤21 days or q3 week dose (6mg/kg) ≤ 42 days from day 1 of treatment; patients who have received trastuzumab within these windows of initiation of therapy should receive an initial dose of 6 mg/kg IV. All subsequent doses are 6 mg/kg IV. There should be no dose adjustment for trastuzumab. Trastuzumab is administered concurrently with cabozantinib on Day 1 of each cycle. For patients who have not previously received trastuzumab, the initial infusion time of trastuzumab (loading dose 8 mg/kg) is approximately 90 minutes.

The initial dose of trastuzumab will be administered over approximately 90 minutes. If this first dose is well tolerated, subsequent infusion times may be shortened to approximately 30 minutes or given per participating site's institutional SOP for trastuzumab administration. If the initial or a subsequent dose is not well tolerated (i.e. fevers, chills, or rigors), subsequent infusion times may be shortened only after a dose is well tolerated.

5.5 General Concomitant Medication and Supportive Care Guidelines

If a participant requires additional systemic anticancer treatment, cabozantinib 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

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 while patient is on study.

Colony stimulating factors (eg, erythropoietin, granulocyte colony-stimulating factors, and peg-filgrastim) are not allowed while patient is on 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.

5.6 Potential Drug Interactions

5.6.1 Cytochrome P450

Data from a clinical drug interaction study (Study XL184 008) show that clinically relevant steady state concentrations of cabozantinib appear to have no marked effect on the area under the plasma drug concentration time curve (AUC) of co administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other

CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184 006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184 007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

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

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

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

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

5.6.2 Drugs Associated with QTc Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see http://www.qtdrugs.org). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

5.6.3 Protein Binding

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

5.6.4 Other Interactions

Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.

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

5.7 Compliance

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

5.8 Study Drug Accountability

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

5.9 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Intolerable side effects the investigator feels may be due to cabozantinib
- Specific conditions described in the medical management Section 6.2.
- The investigator feels it is not in the best interest of the subject to continue on study
- Necessity for treatment with non-protocol approved systemic anticancer therapy
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have cabozantinib discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Subject request to discontinue cabozantinib (with or without concurrent withdrawal of informed consent)
- Significant noncompliance with the protocol schedule in the opinion of the investigator.
- The minimum dose of cabozantinib will be 20 mg po qday. Subjects who cannot tolerate 20 mg po qday will have cabozantinib discontinued.
- Disease progression

- Death
- Intercurrent illness that prevents further administration of treatment
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.
In the event of unusual or life-threatening complications, treating investigators must immediately notify the Principal Investigator, Sara Tolaney, phone: 617-632-2335, or email: **stolaney@partners.org**.

5.10 Duration of Follow Up

Patients who are alive and free of disease progression when they are taken off protocol therapy will be followed until earliest occurrence of disease progression or death, whichever occurs first. Patients who come off cabozantinib for reasons other than disease progression should have a staging scan at the time they go off cabozantinib, and scans should be performed every 9 weeks to look for disease progression. Patients removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients will be followed up for survival after progression until death or lost to follow-up.

5.11 Criteria for Removal from Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS DUE TO CABOZANTINIB

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTCAE Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) 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 cabozantinib, 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

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (eg, pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal [GI] perforation and rectal/perirectal abscess. Arterial thromboembolism (transient ischemic attack [TIA], myocardial infarction [MI]) have been reported rarely.

6.2 Dose Modifications/Delays and Toxicity Management

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of cabozantinib, and for any serious adverse event (SAE) assessed as related to cabozantinib or study procedures, even if the SAE occurs more than 30 days after the last dose of cabozantinib.

Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the cabozantinib may require a dosing delay or reduction(s) in their dose in order to continue with cabozantinib.

Re-escalating cabozantinib after a dose reduction:

- Subjects who required a dose reduction for Grade 4 non-hematologic toxicity should not be re-escalated
- For other related AEs, subjects may be re-escalated to the previous dose at the discretion of the investigator but not sooner than 2 weeks beyond the resolution to Grade ≤ 1 or to the baseline value of AEs.
- If a subject has been dose-reduced , dose re-escalation can only occur to the next higher dose level. Further dose escalation to higher well-tolerated dose levels is allowed only if clinically indicated per investigator's judgment and dose escalation criteria are met with each escalation (e.g. a minimum 2 week interval between escalations)
- If the AEs that previously led to dose reduction(s) recur upon re-escalation, the dose should be reduced again and no further dose escalation will be permitted.
- Dose re-escalation is not allowed for dose reduction triggered by neutropenia or thrombocytopenia.

Additional information for dose delays or dose reductions:

- Dose delays for reason(s) other than AEs related to cabozantinib, such as surgical procedures with no anticancer therapy intent, may be allowed with investigator approval. The acceptable length of interruption will be determined by the investigator.

6.3 Management of Adverse Events

In the absence of an unacceptable cabozantinib-related toxicity and/or clinical signs of disease progression, subjects may continue treatment at the discretion of the investigator. Subjects must be instructed to notify their physician immediately for any and all toxicities.

Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose (see Table 4 below). Dose reductions of more than one dose level are acceptable if agreed to by the Investigator. If cabozantinib of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

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

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

Table 4: Dose Reductions

Starting Dose	**First Level dose Reduction**	**Second Level dose Reduction**
60 mg cabozantinib	Reduce to 40 mg cabozantinib	Reduce to 20 mg cabozantinib

6.3.1 General Guidelines for Non-Hematologic and Hematologic Adverse Events

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

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

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

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

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

Re-escalation to the previous dose, (but not higher than 60 mg/day) may be allowed at the discretion of the investigator but no sooner than 2 weeks beyond resolution of AEs that led to the dose reduction. Dose re-escalation is not allowed for a drug-related dose reduction triggered by myelosuppression or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

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

Table 5: General Approach to the Management of Cabozantinib-Related Non-Hematologic Toxicities

CTCAE v4.0	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level if the AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are intolerable and cannot be adequately managed	Interrupt cabozantinib treatment or dose reduction. Add supportive care as indicated. • If cabozantinib dosing is interrupted, then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	Interrupt cabozantinib treatment and add supportive care as indicated: • For AEs that are easily managed (eg, correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs which occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt cabozantinib treatment until recovery to ≤ Grade 1 or baseline. Then resume treatment with a dose reduction.
Grade 4 AEs (except easily corrected laboratory abnormalities)	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the treating investigator and Principal Investigator, but only with PI approval.

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

Table 6. General Approach to the Management of Hematologic Toxicities

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

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

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

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

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

6.3.2 Gastrointestinal Disorders

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

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced.

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

Nausea and Vomiting

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

Stomatitis and Mucositis

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

During treatment with cabozantinib good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

6.3.3 Hepatobiliary Disorders

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

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

Table 7: Management of Transaminase Elevation

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of liver function tests (LFTs).
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.

Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2 to 3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the treating investigator and Principal Investigator but only with PI approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (ie, Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (ie, AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2 to 3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the treating investigator and Principal Investigator, but only with PI approval.

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

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

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

6.3.4 Fatigue, Anorexia and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated in accordance to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Anorexia and weight loss should be managed in accordance to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced.

6.3.5 Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known, but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase. Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Table 8: Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase weekly • Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.

Table 9: Symptomatic Pancreatitis

Pancreatitis	
Grade 2	• Interrupt treatment • Monitor lipase and amylase weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 2 pancreatitis is at the same dose and Grade 2 pancreatitis recurs, then treatment must be interrupted again until resolution to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 3	• Interrupt treatment • Monitor lipase and amylase weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced dose per investigator judgment.

6.3.6 Skin Disorders

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

Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen

areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study treatment are presented in Table 10.

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

Table 10: Hand-Foot Syndrome

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

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

6.3.7 Thromboembolic Events

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

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

6.3.8 Hypertension

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

Blood pressure should be monitored in a constant position at each visit (either sitting or supine). Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 11. In general, subjects with known hypertension should be optimally managed before study entry. Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes after the first measurement.

Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Table 11: Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg **or** > 100 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ; • Maintain dose of cabozantinib; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be interrupted and/or reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg **or** ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Interrupt and/or reduce cabozantinib by one dose level; • Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications) ; • Monitor subject closely for hypotension; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) **or** ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications; • Monitor subject closely for hypotension; • When SBP < 150 and DBP < 100, restart cabozantinib treatment at one dose level lower; • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 150 systolic or < 100 diastolic, dose of cabozantinib should be reduced further.
Hypertensive emergency or hypertensive encephalopathy	Discontinue all study treatment
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria	

6.3.9 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Management guidelines are provided in Table 12.

Table 12: Management of Treatment Emergent Proteinuria

Severity of Proteinuria (UPCR)	Action To Be Taken
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring.
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• No change in cabozantinib treatment required; • Consider confirming with a 24-hour protein assessment within 7 days; • Repeat UPCR within 7 days and once per week. If UPCR ≤ 1 on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading).
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein; • If ≥ 3.5 on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to ≤ 1.
Nephrotic syndrome	• Discontinue cabozantinib treatment.

UPCR, urine protein to creatinine ratio.

6.3.10 Hemorrhage

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors before initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invades, encases, or abuts major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases;
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis;
- History of clinically significant hemoptysis.

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

6.3.11 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.

6.3.12 GI Perforation/Fistula and Non-GI Fistula Formation

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

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

- Intra-abdominal tumor/metastases invading GI mucosa;

- Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis;
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess;
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing after abdominal surgery or resolution of intra-abdominal abscess must be confirmed before initiating treatment with cabozantinib.

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

Non-GI fistula:

Complications from radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation among subjects undergoing treatment with VEGF pathway inhibitors (eg, bevacizumab). Patients with endotracheal or endobronchial tumor should not be treated with cabozantinib

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

6.3.13 Wound Healing and Surgery

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

6.3.14 Hypophosphatemia

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

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

Clinically relevant hypophosphatemia should be managed in accordance to the dose modification guidelines.

6.3.15 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib and other tyrosine kinase inhibitor treatment as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent (Torino et al. 2009). Preliminary data from ongoing studies indicate that treatment-emergent elevation of thyroid stimulating hormone (TSH) by cabozantinib may be dose-dependent in fashion. Hyperthyroidism has also been reported. Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines.

6.3.16 Guidelines for Prevention of Osteonecrosis of the Jaw

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

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

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case-by-case basis.

6.3.17 Guidelines for Management of Treatment-Emergent Corrected QT (QTc)

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

Other factors which may contribute to QTc prolongation include:

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org);
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels);
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia);
- Medical conditions which can alter electrolyte status eg, severe or prolonged diarrhea.

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

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

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

The Sponsor should be notified immediately of any QTc prolongation event:

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

7 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS DUE TO TRASTUZUMAB

There are no reductions in the trastuzumab dose. If adverse events occur that require holding trastuzumab, the dose will remain the same once treatment resumes.

7.1 Recommendations for Dose Modification of Trastuzumab Based on Cardiac Monitoring

	Asymptomatic LVEF drop	**CTCv3 Grade 3**	**CTCv4 Grade 4**
Trastuzumab	≥10% AND below LLN-Hold, repeat EF in 4-6 weeks, restart if in normal range	Discontinue permanently	Discontinue permanently

- LVEF can be determined by echocardiogram or MUGA but the same method should be used for that patient for all determinations.
- LVEF of greater than 75% at baseline should be re-reviewed and/or at least repeated as it may be falsely elevated.
- Trastuzumab may be restarted if the 4-6 week repeat LVEF has improved such that the hold parameters would no longer apply.
- Patients who have two consecutive or three intermittent "holds" of trastuzumab should have trastuzumab discontinued permanently.
- If trastuzumab is discontinued, patients may still remain on study and receive cabozantinib, if parameters are met for administration of this agent.

7.2 Management of Acute Infusion Syndrome

During the first infusion with trastuzumab, a symptom complex consisting of chills and/or fever is observed commonly in patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusion. These symptoms can be treated with an analgesic/antipyretic such as meperidine, or an antihistamine such as diphenhydramine. Serious adverse reactions to trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases, these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids, and withdrawal of trastuzumab as indicated.

If patients develop an infusion reaction:

- Stop trastuzumab infusion and notify physician.
- Assess vital signs.
- Administer acetaminophen 650 mg PO.

- Consider administration of: meperidine (Demerol®) 50 mg IM, Benadryl® 50 mg IV, Ranitidine 50 mg IV or cimetidine 300 mg IV, and dexamethasone 10 mg IV. It is acceptable to administer meperidine (Demerol®) intravenously.
- If vital signs stable, resume trastuzumab infusion.
- Patients tend not to develop infusion syndromes with subsequent cycles. No standard premedication is required for future treatments if patients have developed an infusion syndrome. Patients may be given acetaminophen prior to treatments.
- If a grade 3 or 4 toxicity occurs during an infusion of trastuzumab, the infusion must be immediately stopped. The patient must be monitored for a minimum of 1 hour after the infusion is stopped. If an outpatient, the patient must be admitted to the hospital for monitoring if the toxicity does not resolve within 3 hours.
- If a grade 3 or 4 toxicity occurs during the post-infusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first noticed. If an outpatient, the patient must be admitted to the hospital for monitoring if the toxicity does not resolve within that hour.

8 DRUG FORMULATION AND STORAGE

8.1 Cabozantinib

8.1.1 Description

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

8.1.2 Form – Cabozantinib Tablets

Exelixis internal number: XL184

Exelixis will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 60-mg, and 20-mg yellow film-coated tablets. The 60-mg tablets are oval, and the 20-mg tablets are round. The components of the tablets are listed in Table 13.

Table 13: Cabozantinib Tablet Components and Composition

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)	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

8.1.3 Storage & Stability

Cabozantinib must be stored at controlled room temperature

8.1.4 Compatibility

Not applicable

8.1.5 Availability

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

8.1.6 Preparation

Not applicable

8.1.7 Ordering

Cabozantinib will be provided by Exelixis.

8.1.8 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.

8.1.9 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.

8.2 Trastuzumab

8.2.1 Product Description

Trastuzumab is commercially available. Trastuzumab Lyophilized Formulation is supplied as a freeze-dried preparation at a nominal content of either 440 mg or 150 mg per vial for parenteral administration (may vary based upon commercial availability). The drug is formulated in histidine, trehalose, and polysorbate 20.

8.2.2 Formulation

Each 440 mg vial is reconstituted with 20mL of Bacteriostatic Water for Injection (BWI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. The reconstituted solution contains 21 mg/mL Herceptin and will be added to 250 mL of

0.9% Sodium Chloride Injection, USP. The reconstituted formulation (440 mg vial) is designed for multiple use. Unused drug may be stored for 28 days at 2ºC-8ºC (36ºF-46ºF).

Each 150 mg vial is reconstituted with 7.4 mL of Sterile Water for Injection (SWFI). The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 ml of 0.9% Sodium Chloride Injection, USP. Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2ºC-8ºC ; discard any unused Herceptin after 24 hours.

8.2.3 Storage

DO NOT FREEZE. Trastuzumab may be sensitive to shear-induced stress (e.g. agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions trastuzumab results in aggregation of the protein and may create cloudy solutions.

Reconstituted trastuzumab should be clear to slightly opalescent and colorless to pale yellow.

9 CORRELATIVE / SPECIAL STUDIES METHODS

9.1 Evaluate c-Met and phosphor-c-Met expression in FFPE tumor tissue (and optional baseline tumor biopsies, if available)

FFPE tissue sections will be deparaffinized prior to antigen retrieval, blocking, and incubation with primary antibodies. Patients will be dichotomized as to whether or not their tumor expresses c-Met and the association between expression and response to cabozantinib will be evaluated.

Please refer to Appendix F for archival tissue guidelines.

9.2 Evaluate the incidence of c-Met positive circulating tumor cells at baseline

Peripheral blood will be collected at baseline for evaluation of c-met amplification in circulating tumor cells (CTCs). Two tubes of whole blood will be collected in CellSave tubes. CTCs will be collected using the automated CellSearch processing technique (Veridex). The captured cells are permeabilized and labeled with cytokeratin CD45

specific antibodies, and the nuclear stain '4-6-Diamidino-2-phenylindole (DAPI), and analyzed by semi-automated counting of appropriately labeled CTCs (Riethdorf et al, 2007). CTCs are defined as CD45 negative and positive for cytokeratin and DAPI. Stained cells are collected by the Veridex system in a "MagNest" cartridge. This cartridge is automatically scanned. Semi-automated counting is performed according to the manufacturer's instructions by a trained pathologist. The MET/CEP 7 bacterial artificial chromosome (BAC) probe will be obtained from Vysis Molecular (Abbot Park, Illinois). BAC MET (RP11-95I20) will be obtained from CHORI (Children's Hospital of Oakland Research Hospital). Labeling will be completed with the Nick Translation Kit (Vysis Molecular (Abbot Park, Illinois). Slides will be maintained in a horizontal position throughout the entire hybridization and washing procedure. Briefly, cells are fixed with methanol-acetic acid (3:1), dehydrated in an alcohol series (50%, 75%, 90%, 100%) and air-dried. Five microliters of the probe mixture are applied, and the slides are covered with cover glass and sealed with rubber cement. Pre-hybridization is done with hybridization buffer without dextran sulfate for 1 hour at 37^{O}C. Denaturation is performed at 94^{o}C for 5 minutes. Hybridization is completed overnight at 37^{o}C. Following hybridization, slides are washed in 1x SSC 3 times for 10 minutes each at 37^{o}C (maintaining the horizontal position), briefly air dried, and counterstained with Vectashield/DAPI (Vector). Two-color FISH slides will be created for each MET amplification analysis. Manual quantification of tumor cells will be performed by determining the total number of whole nuclei (DAPI-positive signals). This will be performed in Dr. Cloud Paweletz's laboratory at Dana-Farber Cancer Institute.

Patients will be grouped as to whether or not their tumor has amplified Met and the association between amplification and response to cabozantinib will be evaluated.

Please refer to Appendix F for specimen collection and shipping guidelines.

9.3 Evaluate potential plasma biomarkers of cabozantinib

Exploratory analyses of potential biomarkers of cabozantinib activity will be performed by measuring proteins in the plasma and circulating cells at baseline, on day 8, day 1 of each cycle of therapy, and, if available, at the end of treatment. 8cc of blood will be collected in purple top (plasma EDTA) vacutainers, with a minimum of 5cc required. Each sample will be shipped on wet ice to the Steele Laboratory at MGH. Blood will be separated by centrifugation into plasma and a cellular phase by standard methods. The plasma will be prepared in standard fashion and stored at –78 degrees Celsius until analysis. After plasma separation, we will use the cellular

fraction for flow cytometric analyses of lymphocytes and myeloid cell populations. We will enumerate cells using CD3, CD4, CD8, CD14, CD25, CD34, CD45, CD56, CD117, CD127 and CD133, using established protocols and an LSR-II flow cytometer available in the Steele Lanboratories. Plasma analysis will be carried out for a panel of circulating angiogenic and inflammatory molecules previously identified as potential biomarkers of response to anti-VEGF therapy in breast cancer patients. They include vascular endothelial growth factor (VEGF), placental-derived growth factor (PlGF), soluble (s)VEGFR1, and basic fibroblast growth factor (bFGF), using 1 multiplex (4-plex) protein array from Meso-Scale Discovery (Gaithersburg, MD), and stromal-derived factor 1α (SDF1α) using ELISA from R&D Systems (Minneapolis, MN). In addition, we will measure the plasma concentration of biomarkers that are related to cabozantinib activity: HGF, s-MET, s-c-KIT and sVEGFR2 using ELISA from R&D Systems (Minneapolis, MN). Finally, we will evaluate biomarkers of tumor hypoxia, by measuring plasma carbonic anhydrase IX **(**CAIX) levels as well as biomarkers of osteoclast and osteoblast activity (plasma C-telopeptide and total alkaline phosphatase) using ELISA from R&D Systems (Minneapolis, MN). Samples will be run in duplicate. The number of circulating cells will be evaluated by using cell counters at routine visits and by flow cytometry in fresh blood samples collected at the same time-points as for plasma measurements.

Please refer to **Appendix F** for specimen collection and shipping guidelines.

9.4 Cerebral blood volume, blood flow, vessel size, tumor infiltration

Two broad approaches have been taken to assess the vascularity of tumors: T1-based, dynamic contrast enhanced (DCE) MRI; and T2-based, termed dynamic susceptibility contrast (DSC) MRI. There are limitations to DCE-MRI, because enhancement depends on multiple factors (blood flow, blood volume, permeability and surface area of the capillary bed). It is therefore important to measure both blood flow and blood volume.

The following measurements will be described at baseline and following the first cycle of cabozantinib (on Cycle 2 Day 1). These analyses are exploratory and hypothesis-generating only. Any promising findings will be further studied in future clinical trials.

- Perfusion MRI Markers

  We will quantitatively describe relative cerebral blood volume/flow (rCBS, rCBF), mean transit time (MTT), and mean vessel diameter from perfusion-weighted MRI (PWI) and arterial spin labeling.

- Permeability

We will measure the permeability surface area product on a voxel-by-voxel basis as well other permeability imaging parameters such as Ve, the volume of extravascular extracellular space.

- Diffusion

  We will measure the full water self-diffusion tensor on a voxel-by-voxel basis. Water mobility can regionally increase due to tissue edema, increased matrix degradation caused by tumor invasion, and/or tumor necrosis. We will also measure tensor fractional anisotropy (FA); FA can be used to define white matter tract directions, and tumor invasion may induce effects like displacement, infiltration, or disruption of white matter tracts.

- Resting State (optional)

  We will measure the default mode connectivity using functional MRI to assess the infiltration, or disruption of white matter tracts.

- MR Spectroscopy (optional)

  We will obtain MRS to look at tumor metabolites and tumor infiltration

9.5 Pain Assessments

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 B), 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. The participant will complete this pain questionnaire each day for a 7-day interval within 14 days before the first dose of cabozantinib and at 7-day intervals during Week 3 and the last week of the cycles that patients are scanned on (ie end of cycle 2, 4, 6, 9, 12, etc.) until the date of the participant's last follow-up visit.

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.

The pain questionnaire and analgesic medication diary will be due on the last week of the cycles that patients are scanned on (ie end of cycle 2, 4, 6, 9, 12, etc.)until the date of the participant's last follow-up visit. The first pain questionnaire completed can be used to report pain that the participant experienced the week prior to the date of the study consent signature.

9.6 Tumor biopsies

With agreement of the investigator and with the participant's consent tumor tissue samples may be optionally collected, preferentially, during the screening period (preferably 1-2 weeks prior to initiation of cabozantinib treatment).

Please refer to **Appendix F** for specimen collection and shipping guidelines.

Tumor analyses may involve evaluation of the signaling pathways related to cabozantinib targets (eg, VEGFR, MET, KIT, RET) and include methods such as genotyping, fluorescence in situ hybridization (FISH) and/or Immuno-histochemistry (IHC). Mutation and/or amplification status of disease-specific tumor-promoters or suppressors may also be determined to characterize the potential impact on response or resistance to cabozantinib (eg, HER2, EGFR, KRAS, NRAS, BRAF, PTEN, PIK3CA, TP53). Broader genome-wide copy number and mutation profiling may also be conducted. For paired tumor biopsies pharmacodynamic markers such as pMET/MET, pVEGFR2/VEGFR2, pERK/ERK, pAKT/AKT and pKIT/KIT may also be analyzed by IHC.

9.7 Blood sample collection

Blood will be collected at baseline and the end of treatment for the analysis of cfDNA and to be processed by the DF/HCC Clinical Trials Core Laboratory and then banked in the DF/HCC Clinical Trials Core laboratory for future research purposes.

One 10 ml of whole blood will be collected in Streck Tubes. The blood sample will be collected and processed at baseline and at the end of treatment for evaluation of cfDNA. Tubes are provided by the Sponsor as needed.

If the blood collection is missed at baseline or at the time of progression, then the blood will be collected at a future appointment. The banked samples will be used to analyze DNA, RNA and protein in future studies.

Please refer to **Appendix F** for specimen collection and shipping guidelines and **Appendix H** for additional processing details specific to the laboratories at Dana-Farber Cancer Institute.

10 STUDY CALENDAR

All assessments must be performed prior to administration of any study medication.

Table 14: Study Calendar

	Pre-treatment	21 Day Cycles								
Assessments/ Procedures	**Screening[A]**	**C1 D1**	**C1 D8 (± 2 days)**	**C 2 D1 (± 4 days)**	**C3 D1 and Subsequent Odd Cycles Day 1 (± 4 days)**	**C4 D1 (± 4 days)**	**C6 D1 and Subsequent Even Cycles Day 1 (± 4 days)**	**Every 2 Cycles (days 16-22)**	**Every 4 Cycles (days 16-22)**	**End of Cabozantinib**
Informed consent	X									
Inclusion/ exclusion criteria	X									
Demographics	X									
Medical and cancer history	X			X	X	X	X			X
Concomitant medications	X	X	X	X	X	X	X			X
Complete physical examination	X	X[B]	X	X	X	X	X			X
Height	X									
Weight	X	X	X	X	X	X	X			
Vital signs[C]	X	X[B]	X	X	X	X	X			X
ECOG performance status	X	X[B]	X	X	X	X	X			X
12-lead EKG [D]	X			X		X				
MUGA or echocardiogram[E]	X								X[E]	
Neurological examination[F]	X		X	X	X	X	X			X
CBC w/ differential and platelets	X	X[B]	X	X	X	X	X			X
Coagulation studies (PT/INR and PTT)	X	X[B]		X	X	X	X			X
Serum chemistry[G]	X	X[B]	X	X	X	X	X			X
Amylase/lipase	X	X[B]		X	X	X	X			X
Urine protein and creatinine[H]	X	X[B]			X					X

	Pre-treatment	21 Day Cycles								
Assessments/ Procedures	**Screening[A]**	**C1 D1**	**C1 D8 (± 2 days)**	**C 2 D1 (± 4 days)**	**C3 D1 and Subsequent Odd Cycles Day 1 (± 4 days)**	**C4 D1 (± 4 days)**	**C6 D1 and Subsequent Even Cycles Day 1 (± 4 days)**	**Every 2 Cycles (days 16-22)**	**Every 4 Cycles (days 16-22)**	**End of Cabozantinib**
TSH	X	X[B]			X					X
Research blood draw for CTC collection[I]	X									
Research blood draw for Plasma biomarkers[J]	X		X	X	X[J]	X[J]		X[J]		X[J]
Research blood draw for cfDNA[K]	X									X[K]
Serum/urine pregnancy test[L]	X									
Baseline Findings (CTCAE v.4.0)	X									
Brain MRI[M]	X				X			X[M]		
Research MRI sequences[N]	X			X						
Non-CNS tumor evaluation (MRI or CT and clinical assessment of visible, palpable lesions)[M]	X				X			X[M]		
Bone scan[O]					X			X[M]		X[M]
CA 27.29 or CA15.3	X	X[B]		X	X	X	X			X
Adverse events[P]	X	X	X	X	X	X	X			X
Drug diary		X	X	X	X	X	X			
Survival follow-up										X[Q]
Optional biopsy[R]	X									
7-day pain questionnaire[S]	X			X	X[S]					
7-day analgesic medication diary[S]	X			X	X[S]					
Cabozantinib[T]		X	X	X	X	X	X			

	Pre-treatment	21 Day Cycles								
Assessments/ Procedures	**Screening[A]**	**C1 D1**	**C1 D8 (± 2 days)**	**C 2 D1 (± 4 days)**	**C3 D1 and Subsequent Odd Cycles Day 1 (± 4 days)**	**C4 D1 (± 4 days)**	**C6 D1 and Subsequent Even Cycles Day 1 (± 4 days)**	**Every 2 Cycles (days 16-22)**	**Every 4 Cycles (days 16-22)**	**End of Cabozantinib**
Trastuzumab[U]		X		X	X	X	X			

[A] Laboratory tests must occur within 14 days before initial dose of cabozantinib. All other screening assessments must occur within 28 days before initial dose of cabozantinib (with the exception of the baseline research MRI sequences, which must be ≤ 7 days of C1D1 dose). 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 cabozantinib, 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 cabozantinib. All pre-treatment criteria listed in Section 5.2 must be met in order to begin cabozantinib on Cycle 1 of Day 1.

[C] Includes blood pressure, pulse, respiratory rate, temperature, weight

[D] Three EKGs must be performed at screening. To be eligible, the patient must have an average QTcF of ≤ 500 msec on three consecutive results.

[E] Only performed in HER2-positive patients currently taking trastuzumab. Evaluation of LVEF to occur at baseline and every 4 cycles. When possible, the same modality (e.g. MUGA or ECHO) should be performed for consistency in measurements.

[F] Neurologic examination worksheet (Appendix E) to be completed at baseline and at each study visit, except for Cycle 1 Day 1 the neurological examination will be on Cycle 1 Day 8.

[G] Complete serum chemistry panel includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, creatinine, glucose, magnesium, potassium, phosphorus, sodium, total bilirubin, total protein. Electrolytes do not need to be collected as part of the eligibility assessment (K, Phos, Ca, Mg).

[H] Spot urine protein and urine creatinine

[I] At baseline, 2 tubes of whole blood will be collected in 10 ml CellSave tubes for CTC analysis. If this is not performed at screening, then it can be collected on C1D1 prior to the start of treatment.

[J] At baseline and at C1D8, C2D1, C3D1, C4D1, C5D1, C6D1 and then every 2 cycles, and at end of treatment, two 10 ml purple top tubes (plasma EDTA) will be collected (minimum of 5 cc of blood in each) at each visit. The purple top tubes will be shipped on wet ice to the Steele Laboratory at MGH. If this is not performed at screening, then it can be collected on C1D1 prior to the start of treatment. After 18 weeks (6 cycles) research blood collection for plasma biomarkers should occur at the same time scans are reviewed after a restaging. After 18 weeks, frequency of restaging scans is reduced to once every 3 cycles (item M above), therefore draws will occur on C7D1, C10D1, C13D1, etc.

[K] At baseline and at the end of treatment, 1 tube of whole blood will be collected in a 10 ml Streck tube for cfDNA analysis. If sample collection is missed for any reason at baseline or at the end of treatment then the sample should be drawn at a future appointment.

[L] For women of child bearing potential. This must be performed within 14 days of C1D1.

[M] Clinical Brain MRI at screening and non-CNS tumor evaluation must be performed within 28 days of Cycle 1 Day 1. Clinical Brain MRI and non-CNS tumor evaluation scans will then be completed within 7 days prior to Cycle 3 Day 1, Cycle 5 Day 1, and Cycle 7 Day 1. Patients with stable or responsive disease after completion of 6 cycles may have the frequency of restaging scans reduced to once every 3 cycles. For patients who come off cabozantinib for any reason other than disease progression, they will need to undergo a scan at the time they come off cabozantinib, and continue undergoing scans every 9 weeks. They will also need to have a follow-up visit every 6 months.

[N] The research MRI sequences will be performed at Massachusetts General Hospital, Charlestown Navy Yard at Baseline (≤ 7 days of Cycle 1 Day 1), and at Cycle 2 day 1 (prior to dose treatment that day). The study coordinator will obtain a copy of the MRI scan to be archived at DFCI. Contact name for Massachusetts General Hospital Charlestown Navy Yard is Stephanie Salcedo (ssalcedo@partners.org).

[O] Bone scans should be performed in any patient with known bone metastases.

[P] Adverse events information will be collected at study visits and may, in addition, be collected over the phone. For patients who come off cabozantinib for progressive disease, an end of Study Visit should be completed within 30 days (+/- 7 days) of last dose of study drug.

[Q] Follow-up every 6 months or until death

[R] For patients that consent to optional biopsy only, preferentially performed 1-2 weeks prior to receiving first dose of study drug.

[S] The participant will complete the pain diary and medication diary each day for a 7-day interval within 14 days of the first dose of cabozantinib and at 7-day intervals during Week 3 and the last week of the cycles that patients are scanned on (ie end of cycle 2, 4, 6, 9, 12, etc). Pain Questionnaire and Analgesic Medication Diary will also be due the last week of cycles that patients are scanned on (end of Cycle 2, 4, 6, 9, 12, etc.)The first pain questionnaire completed can be used to report pain that the participant experienced the week prior to the date of the study consent signature. Analgesic medications to be recorded on the diary include narcotics and corticosteroids used to treat pain symptoms.

[T] Cabozantinib will be given orally once daily

[U] Trastuzumab will be given to HER2- positive patients (cohorts 1)

11 MEASUREMENT OF EFFECT

Response in the CNS and non-CNS will use RECIST 1.1. Volumetric assessments of CNS response will also be conducted. Response and progression in non-CNS sites will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Therasse, 2000). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria. For the purposes of this study, participants should be re-evaluated for response every 6 weeks. Patients with stable or responsive disease after completion of 6 cycles may have the frequency of restaging scans reduced to once every 3 cycles. In addition to a baseline scan, confirmatory scans should also be obtained 3 weeks following initial documentation of objective response.

Response in the CNS and in non-CNS sites will be evaluated and recorded separately in this trial.

11.1 Definitions

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

Evaluable for objective response. Only those participants who have received at least one dose of therapy 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 1 will also be considered evaluable.) All participants who receive at least one dose of cabozantinib will be considered in the denominator for calculation of objective response rate.

11.2 Disease Parameters

Measurable disease.

Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter $\geq$20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or $\geq$10 mm with spiral CT

scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes).

Malignant lymph nodes.

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 followed.

Non-measurable disease.

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered 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, should be identified as target lesions and recorded and measured at baseline. Lesions must be accurately measured in 1 dimension. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). For CNS and non-CNS sites, the sum of the longest diameter (LD) for all target lesions will be calculated

and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response in CNS and non-CNS sites. RECIST 1.1 criteria will be used to assess overall response rates for CNS target lesions as the primary endpoint. In addition, we will also report non-CNS response rates according to RECIST 1.1 criteria and CNS lesion responses according to volumetric and composite criteria.

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 target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions.

All other lesions including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include bone lesions that do not meet the requirements of the last paragraph, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques are considered non-target lesions.

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline non-CNS evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Clinical brain MRI at screening will be performed within 28 days of Cycle 1 Day 1 and research MRI sequences will be performed within 7 days of Cycle 1 Day 1.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Methods of Evaluation for CNS Measurable Disease

MRI Brain: Imaging with MRI brain is required for all participants on study to evaluate brain lesions. MRI images will include T1-weighted images with and without gadolinium contrast, T2-weighted images, and FLAIR (fluid attenuated inversion recovery) images.

Methods of Evaluation for Non-CNS Measurable Disease

Clinical lesions. Measurable skin lesions will be documented by color photography, including use of a ruler to estimate the size of the lesion.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

FDG PET and PET/CT. 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 (Shankar et al., 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 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.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response.

11.4 Response Criteria

11.4.1 Response Criteria for Target Lesions (RECIST 1.1)

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

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

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

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

11.4.2 Response Criteria for Non-Target Lesions (RECIST 1.1)

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

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.4.3 Evaluation of New Lesions

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

11.4.4 CNS Volumetric & Composite Response Criteria

RECIST 1.1 criteria will be used to determine response but volumetric/composite response will also be done as an exploratory study.

CNS Complete Response (CR): All of the following must be satisfied:

- Complete resolution of all measurable (≥ 1 cm diameter) and non-measurable brain metastases
- No new CNS lesions (new lesion defined as ≥ 6 mm diameter)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms

- No progression of systemic (non-CNS) disease as assessed by RECIST

CNS Partial Response (PR): All of the following must be satisfied:

- ≥ 50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline
- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST

CNS Stable Disease (SD): All of the following must be satisfied:

- < 50% reduction in the volumetric sum of all measurable (≥ 1 cm diameter) brain metastases compared to baseline, and not fulfilling the criteria for progressive disease
- No progression of non-measurable lesions
- No new lesions (new lesion defined as ≥ 6 mm)
- Stable or decreasing steroid dose
- No new/progressive tumor-related neurologic signs or symptoms
- No progression of systemic (non-CNS) disease as assessed by RECIST

Note: CNS lesions were initially evaluable (≥ 1 cm diameter) at baseline and have decreased in size on trial therapy to < 1 cm diameter will continue to be assessed volumetrically for response.

CNS Progression (PD): Patients will be considered to have PD if **ANY** of the following are satisfied:

- ≥40% increase in the volumetric sum of all measurable lesions as compared to the smallest volume since protocol-based therapy was initiated, OR
- Progression of non-measurable lesions*, OR
- New lesions (new lesion defined as ≥ 6 mm), OR
- Increasing steroid requirement (As CNS progression is an eligibility requirement, increasing steroid dose within 4 weeks after study entry will not necessarily constitute disease progression), OR
- New/progression tumor-related neurologic signs and symptoms (NSS) except for transient worsening lasting ≤ 14 days. (As CNS progression is an eligibility

requirement, worsening of NSS within 4 weeks after study entry will not necessarily constitute disease progression), OR

- Progression of systemic (non-CNS) disease as assessed by RECIST

*Note: Progression of non-measurable (non-target) CNS lesions is defined as follows:

- A lesion initially at baseline ≤ 5 mm in diameter that increases to ≥ 10 mm in diameter, or
- A lesion initially at baseline 6-9 mm in diameter that increases by at least 5 mm in diameter.

These criteria were chosen to minimize classifying subjects as having progressive disease due to MRI sampling error, given an MRI slice thickness of 3 mm.

Table 15: Summary of Composite Criteria for CNS Response

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Qualifying Criteria	All	All	All	Any
Brain lesions (volumetric MRI)				
Target	CR	≥ 50% volume decrease	< 50% volume decrease	≥ 40% volume increase
Non-target	None/CR	None/no progression		Progression
New	None			Yes
Steroids	Stable or decreasing			Increasing dose
Neurological signs/symptoms	Stable or improving			New or worsening
Systemic disease (RECIST 1.1)	No progression			Progression

11.4.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria based on RECIST 1.1.

Table 16: Criteria for Patients with Measurable Disease (i.e., Target Disease)

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

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

11.4.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.4.7 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or time of death from any cause, whichever comes first. Included in the definition of progression for PFS are: objective progression of CNS lesions on MRI, neurologic deterioration leading to study discontinuation, global deterioration of health status requiring discontinuation of treatment, and death. For neurologic symptoms, the default will be to assume that worsening of neurologic symptoms requiring discontinuation of treatment is related to progressive disease. However, it is anticipated that some patients may discontinue due to peripheral neuropathy or other neurologic symptoms that are more likely related to cumulative drug toxicity rather than CNS progression. For patients who are taken off of protocol treatment for a reason(s) other than progression, the date of PFS will be censored at the date of last staging study (either while on or off protocol therapy) on which the patient is documented not to have progressed, or the date of initiation of alternative anti-cancer therapy, whichever comes first.

11.4.8 Response Review

All CNS and non-CNS responses will be reviewed by an independent radiologist as part of the DF/HCC Tumor Imaging Metrics Core (TIMC) facility. CNS response will be assessed centrally using the RECIST 1.1 and volumetric criteria outlined. Non-CNS scans will also be assessed centrally using RECIST 1.1 and recorded in the CRF by individual site personnel.

11.5 Neurological Signs and Symptoms (NSS)

Tumor-associated NSS will be recorded on Appendix E at each study visit.
Improvement or worsening of non-tumor associated NSS will not constitute a change in NSS.

Improvement of NSS will be defined if all of the following are satisfied:

- Decrease by 1 or more grades from baseline of any tumor-related NSS, with confirmation at least 3 weeks (1 cycle) later
- No development or worsening in any tumor related NSS during this interval
- Stable or decreasing steroids during this interval

In addition, Appendix E contains a global question for the treating investigator, asking whether a patient's neurological status is improved, stable or worse. The response to this question will be analyzed in relation to the itemized portion of the NSS worksheet, in order to further evaluate the utility of the worksheet in evaluating NSS longitudinally over time.

12 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Definitions

12.1.1 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 cabozantinib 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.

12.1.2 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 severe 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 disability/incapacity. Disability is defined as a substantial disruption of a person's 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 **not** 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

12.1.3 Expectedness

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

Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's

Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

12.1.4 Attribution

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

- Not Related: A not-related AE is defined as an AE that is not associated with the cabozantinib and is attributable to another cause.
- Related: A related AE is defined as an AE where a causal relationship between the event and the cabozantinib is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (eg, evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and cabozantinib.

12.2 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.

12.3 Expedited SAE Reporting Guidelines

12.3.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

All serious adverse events that occur after the initial dose of cabozantinib, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 1 business day 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 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Sara Tolaney, MD, MPH
Phone: 617-632-2335
Email: stolaney@partners.org
Fax: 617-632-1930

12.3.2 Serious Adverse Event Reporting to Exelixis

All serious adverse events that occur after the initial dose of cabozantinib, during treatment, or within 30 days of the last dose of treatment that meet the criteria per DF/HCC AE policy must be reported to Exelixis on the local institutional SAE form. Forms should be sent to the following within two business days:

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

- This report must be submitted by the study site to Exelixis or designee within two business days, even if it is not felt to be drug related.
- The investigator agrees to provide supplementary information requested by the Exelixis Drug Safety personnel or designee.
- Pregnancy, although not itself an SAE, should also be reported on an SAE form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

12.3.3 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.

12.4 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).

12.5 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the cabozantinib.

Unexpected fatal or life-threatening experiences associated with the use of the cabozantinib 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 cabozantinib will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm. A hard copy of the form will also be submitted to the FDA.

12.6 Reporting to the Hospital Risk Management

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

12.7 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 and their respective IRB 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.

13 DATA AND SAFETY MONITORING

13.1 Data Reporting

13.1.1 Method

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

13.1.2 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

13.2 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; current dose level information; DLT information; 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.

13.3 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, 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.

14 REGULATORY CONSIDERATIONS

14.1 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.

14.2 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.

14.3 Ethics

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

- 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 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.

14.4 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.

14.5 Records Retention

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

15 STATISTICAL CONSIDERATIONS

15.1 Study Design / Endpoints

This is a two-stage phase 2 study of XL184 for HER2-positive metastatic breast cancer with known brain metastases, and a pilot study of XL184 for ER+ and TN breast cancer with known brain metastases.

The primary endpoint is response, defined as a confirmed CR or confirmed PR per CNS objective response. Patients who do not achieve a confirmed CR or confirmed PR will be considered non-responders. Assuming the study does not terminate early and all patients enrolled begin protocol therapy, the 95% CI for the response rate will be determined accounting for the two-stage design.

All other analyses are exploratory with no plans for formal hypothesis testing given the limited sample size. Analyses will treat as categorical variables c-MET amplification in CTC's, or marker levels that can be categorized using established cutpoints. Variables will be tabulated by RECIST response. For markers without an established cutpoint, analyses will involve summary statistics by RECIST response. PFS and OS, as defined in Section 11.4.5, will be described using the method of Kaplan-Meier. The point estimate of median PFS and OS, as well as estimates of PFS and OS at other time points, will be presented with 95% confidence intervals derived using log(-log(PFS)) methodology.

15.2 Sample Size / Accrual Rate

There are no data on the response rate to XL184 in patients with metastatic breast cancer and brain metastases. A true rate of 30% among predominantly pretreated patients with HER2-positive metastatic breast cancer would be considered worthy of further study. A true rate of 5% or less would not be of clinical interest. This is a one-arm two-stage

design to evaluate the efficacy of XL184 in patients with HER2-positive metastatic breast cancer and brain metastases. The sample size was chosen to have high power (90%) with a Type I error no more than 10%.

In the first stage, 7 patients will be enrolled. If there is at least 1 response, accrual will continue to the second stage where up to 14 additional patients will be enrolled. If at least 3 of these 21 patients have a response rate, the regimen will be considered worthy of further study. With this design, the probability of stopping the trial early is 70% if the true response rate is 5%, and 8% if the true response rate is 30%. If the true response rate is 5%, the chance the regimen is declared worthy of further study is 10% and if the true response rate is 30% the chance that the regimen is declared worthy of further study is 90%.

Update: As of October 20, 2015, there have been no confirmed CNS objective responses by RECIST 1.1 in the first seven patients enrolled in the HER2+ cohort. There has been one volumetric partial response (PR) in the brain, along with a partial response (PR) in the body (Table 17). In addition, patients have remained on trial for a significant amount of time, with two of seven patients on study for 9 cycles, and one on for 8 cycles, with continued stable disease. Given that there seems to be t meaningful clinical benefit received with the agent, we felt further study of this agent is warranted in this population. Thus, an additional 14 patients will be enrolled to a maximum of 21 HER2+ patients in order to have more precise estimates of the efficacy of cabozantinib in patients with metastatic breast cancer and brain metastases.

Table 17: **Data for the HER2+ Cohort as of October 20, 2015**

HER2+ Cohort							
ER/PR/HER2 status	On/off	Cycles	Dose red (Y/N)	TIMC best response (%)			Reason Off
				Brain		Body	
				RECIST	Volume		
-/-/+	Off	2	N	SD (-13.1)	SD (-43.9)	PD (75.2)	Body PD
+/+/+	Off	9	Y (20mg)	SD (-5.9)	SD (6.3)	SD (-8.9)	Brain and body PD
-/-/+	Off	5	N	SD (-9.8)	SD (-39.5)	SD (0.0)	Clinical PD
+/+/+	Off	9	Y (40mg)	SD (-21.7)	SD (-46.3)	NP (0.0)	Brain PD
+/-/+	Off	4	Y (40mg)	SD (-6.8)	SD (-41.3)	PR (-42)	Vol. PD and clinical PD
-/-/+	**On**	**8**	**N**	**SD (-0.3)**	**SD (-17.5)**	**NP (0.0)**	**N/A**
+/-/+	**On**	**5**	**Y (40mg)**	**SD (-8.7)**	**PR (-72.6)**	**SD (0.0)**	**N/A**

The primary analysis will declare that under the Simon two-stage design, we are unable to reject the null hypothesis for the true CNS objective response rate in HER2+ patients. Secondary analysis will be estimation-only, and report all endpoints of clinical activity (best overall response by RECIST, best overall CNS volumetric response, best response in the body, progression-free survival) with 95% confidence intervals. With 21 evaluable HER2+ patients, the maximum half-width of a confidence interval for response rates is 0.22.

Eight patients with ER-positive metastatic breast cancer and brain metastases and 8 patients with triple-negative metastatic breast cancer and brain metastases will be enrolled in two pilot cohorts for studying the efficacy of XL184 in patients with those two subtypes of metastatic breast cancer. If the true response rate is 30% in ER+ and TN disease, the probability that no responses are seen in 8 patients is 5.7%. The table below gives exact 95% confidence intervals for seeing 1 to 3 responses in 8 patients. Even if the regimen is concluded as ineffective in interim analysis of the HER2-positive cohort, accrual in pilot cohorts will continue until reaching the goal accrual.

Table 18: Estimated 95% Confidence Interval for Events

Sample Size	Number of Response	Response Rate	95% CI
8	1	12.5%	0.3-52.7%
8	2	25.0%	3.2-65.1%
8	3	37.5%	8.5-75.5%

Accrual is estimated to be 1-2 patients per month. Total accrual time is estimated to be approximately 18-24 months.

15.2.1 Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

15.2.2 Evaluation of response

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Ineligible patients will be excluded. 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.

16 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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APPENDIX A: 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.

Pain Questionnaire and Analgesic Medication Diary Due Dates for Appendix B and Appendix C

The participant will complete the pain diary and analgesic medication diary each day for a 7-day interval within 14 days of the first dose of cabozantinib and at 7-day intervals during Week 3 and the last week of the cycles that patients are scanned on (ie end of cycle 2, 4, 6, 9, 12, etc) The pain questionnaire and analgesic medication diary will also be due the last week of cycles that patients are scanned on (end of Cycle 2, 4, 6, 9, 12, etc.) The first pain questionnaire completed can be used to report pain that the participant experienced the week prior to the date of the study consent signature. Analgesic medications to be recorded on the diary include narcotics and corticosteroids used to treat pain symptoms. As follows the pain questionnaire and analgesic medication diary should be completed by the participant and then brought with them to next appointment:

- Questionnaire and diary completed during Cycle 1 Day 15-21 (Week 3); then they will be due on Cycle 2 Day 1 (Week 4).
- Question and diary completed during Cycle 2 Day 15-21 (Week 6); then they will be due on Cycle 3 Day 1 (Week 7).
- Questionnaire and diary completed during Cycle 4 Day 15-21 (Week 12); then they will be due on Cycle 5 Day 1 (Week 13).
- Questionnaire and diary completed during Cycle 6 Day 15-21 (Week 18); then they will be due on Cycle 7 Day 1 (Week 19).

APPENDIX B: PAIN QUESTIONNAIRE

Participant ID number:

Date: _____ Participant Signature: _____

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**?	○	○	○	○	○	○	○	○	○	○	○

Participant ID number:_____ Date: _____

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
- Not Applicable (first time completing this form)

APPENDIX C: 7-DAY ANALGESIC MEDICATION DIARY

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)	**Date:** __/__/__ (mm/dd/yy)	**Date:** __/__/__ (mm/dd/yy)	**Date:** __/__/__ (mm/dd/yy)	**Date:** __/__/__ (mm/dd/yy)	**Date:** __/__/__ (mm/dd/yy)	**Date:** __/__/__ (mm/dd/yy)
			# Taken	**# Taken**	**# Taken**	**# Taken**	**# Taken**	**# Taken**	**# Taken**
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								
	☐ Pill ☐ Patch ☐ Injection								

Patient Signature:___________: Date:______________________

APPENDIX D: PARTICIPANT'S MEDICATION DIARY

Participant's Name_____ (*initials acceptable)*
Participant ID_____
Protocol #: _____ **Cycle #:** _____ **Study Drug:** CABOZANTINIB **Your Dose:** _____

INSTRUCTIONS FOR TAKING YOUR CABOZANTINIB:

1. Complete one form for each cycle of treatment (Cycle = 21 days).
2. You will take CABOZANTINIB tablets via mouth once a day. You should take the tablets each morning after you have fasted for 2 hours (no food or drink with the exception of water). You should continue to fast for 1 hour after taking your CABOZANTINIB. CABOZANTINIB should be taken with a full glass of water (8 oz minimum) and consumed over as short a time as possible. Please swallow the tablets as a whole and do not crush, chew or dissolve in water. Grapefruit and Seville oranges must be avoided while on study.
3. If you forget to take your daily CABOZANTINIB dose:
   - If it has been more than 12 hours since missing your scheduled dose, do NOT take your missed dose.
   - If it has been less than 12 hours since missing your scheduled dose, take your dose immediately and continue taking your dose at your regular time the next day.
4. If you vomit your dose, do NOT retake your dose. Wait until the next day to take your next scheduled dose. Remember to tell your study doctor or nurse at your next visit which dose(s) you missed.

INSTRUCTIONS FOR COMPLETING THIS FORM:

Record the date, the number of tablets of each size of tablet that you took, and when you took them. If you have any comments or notice any side effects, please record them in the Comments column. **Please bring this form and your bottles (even if they are empty) of CABOZANTINIB when you return for each appointment.**

Day	Date	Time of dose	# of tablets taken		Comments
			mg	mg	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					

Participant's signature _____ **Date:** _____

APPENDIX E: NEUROLOGICAL SIGNS AND SYMPTOMS

Neurological Examination Worksheet

(to be completed at baseline and at the end of each 3-week cycle)

Please note if signs/symptoms are thought related or not-related to patient's brain metastases

Patient _____ Examiner _____ Date_____

Level of consciousness (check one)

___ Normal
___ Somnolence or sedation not interfering with function
___ Somnolence or sedation interfering with function, but not interfering with ADLs
___ Obtundation or stupor, difficult to arouse; interfering with ADLs
___ Coma

Neurological Symptoms (check if present, and specify CTCAE grade)

** *if asymptomatic, check here* ___

Headache	___	present, specify grade _____
Dizziness/lightheadness	___	present, specify grade _____
Vertigo	___	present, specify grade _____
Nausea/vomiting	___	present, specify grade _____
Visual problems	___	present, specify grade _____
Seizure	___	present, specify grade _____
Other	___	absent, ___ present, specify grade _____

Cranial nerves II – XII[+]

___ Normal
___ Present, not interfering with ADLs
___ Present, interfering with ADLs
___ Life-threatening, disabling
\+ *If abnormal, please specify which cranial nerve(s) affected* _____

Language

___ Absence of dysphasia or aphasia
___ Awareness of receptive or expressive aphasia, not impairing ability to communicate
___ Receptive or expressive dysphasia, impairing ability to communicate
___ Inability to communicate

Sensation**

___ Normal
___ Loss of deep tendon reflexes or paresthesia, but not interfering with function
___ Objective sensory loss or paresthesia interfering with function, but not with ADLs
___ Sensory loss or paresthesia interfering with ADLs
___ Permanent sensory loss that interferes with function
** *If abnormal, please specify location/distribution* _____

Neurological Examination Worksheet

(pg. 2 of 2)

Patient _____ Examiner _____ Date_____

Strength*

R upper extremity	___ Normal	___ Abnormal; please specify _____
L upper extremity	___ Normal	___ Abnormal; please specify _____
R lower extremity	___ Normal	___ Abnormal; please specify _____
L lower extremity	___ Normal	___ Abnormal; please specify _____

**If abnormal, please specify muscle group and grade according to the scale below: (e.g., biceps, grade 2)*

- Grade 1 = asymptomatic with weakness on physical exam
- Grade 2 = symptomatic and interfering with function, but not interfering with ADLs
- Grade 3 = symptomatic and interfering with activities of daily living
- Grade 4 = bedridden or disabling

Ataxia***

R upper extremity (finger-to-nose testing)	___ Normal	___ Abnormal; specify grade ___
L upper extremity (finger-to-nose testing)	___ Normal	___ Abnormal; specify grade ___
Gait	___ Normal	___ Abnormal; specify grade ___
Balance (Romber)	___ Normal	___ Abnormal; specify grade ___

**** If any of above abnormal, please assign grade using the following criteria*

- Grade 1 = asymptomatic but abnormal on physical exam, and not interfering with function
- Grade 2 = mild symptoms interfering with function, but not interfering with ADLs
- Grade 3 = moderate symptoms interfering with ADLs
- Grade 4 = bedridden or disabling

In the opinion of the treating physician, overall are the patients ***tumor-related* neurological signs and symptoms worsening, stable or improved (please check one)?**

___ Worsening
___ Stable
___ Improved

Is the patient currently taking corticosteroids?

___ Yes
___ No

If yes, please list name of medication and dose (e.g. decadron, 4 mg QD) _____

APPENDIX F: RESEARCH SPECIMEN COLLECTION/SHIPPING GUIDELINES

Procedures for Collecting and Shipping Circulating Tumor Cells (CTCs):
Automated CellSearch™ processing technique (Veridex). 8 mls of whole blood is collected in 10 ml CellSave tubes™. Samples must be kept at room temperature and must be PROCESSED within 96 hours of draw.

SAMPLE COLLECTION
1. Ensure that peripheral blood collection occurs prior to administration of i.v. therapy.
2. The blood sample must be collected in a CellSave preservative tube. Label the tube with the sample identifier/number, protocol number, and submitting investigator.
3. Collect at least 8 ml of blood. Gently invert the tube 8 times to prevent clotting immediately after filling the tube.
4. Do not submit clotted samples.

SAMPLE SHIPPING
1. The blood sample must be transported and stored 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 the tube (along with the baseline CTC sample) AT ROOM TEMPERATURE to:

For sample drawn at institution other than DFCI, ship to:
Madeline Tenenbaum450 Brookline Ave., Mailstop DA157
Boston, MA 02215

- Please email Madeline Tenenbaum(madeline_tenenbaum@dfci.harvard.edu) the day before with sample information and tracking information.
- CTC blood samples should not be drawn the day before a holiday weekend.
- Email CTC core and cc Elena Ivanova and Masahiko Yanagita to co-ordinate (if sample coming from site other than DFCI, also cc DFCI CRCMadeline Tenenbaum), BWHPathologyCTCLab@partners.org; evivanova@partners.org; myanagita@partners.org; madeline_tenenbaum@dfci.harvard.edu

Please include the following info in the email:

Protocol: 14-359
Patient: _____
MRN: _____
Time point: BL / C1D1
Date of draw: _____
Time of draw: _____
Enumeration, profile, or both: Profile kit (tube)

- DFCI CRC will take tubes and requisition to CTC core for same day or next day early morning processing. (For Friday patients tubes may be processed at CTC core on Monday depending on whether Elena prefers that)
- CTC core should email Elena when tubes are ready for pick up. Samples will be processed in Dr. Cloud Paweletz's laboratory at the Dana-Farber Cancer Institute.

Procedures for Collecting and Shipping Plasma Biomarkers

Exploratory analyses of potential biomarkers of cabozantinib activity will be performed by measuring proteins in the plasma and circulating cells at the following timepoints:

- Baseline
- Cycle 1 Day 8
- Day 1 of each cycle of therapy (Cycles 1-6)
- When scans are reviewed after restaging after Cycle 6 (Day 1 every 3 cycles after 18 weeks have passed)
- At the end of treatment (if available)

8cc of blood will be collected in purple top (plasma EDTA) vacutainers, with a minimum of 5cc required. Each sample will be de-identified and shipped on wet ice to the Steele Laboratory at MGH (via courier from DFCI).

CRC to Email Anna Khachatryan (akhachatryan@partners.org) and Julia Kahn (jakahn@partners.org) a list of expected samples for next week. For example:

12-431	00011	R-W	C3D1	2 purple tops	11/11/2013	10:20 AM

Procedures for Collecting and Shipping cfDNA:

One 10 ml Streck tube will be collected and processed at baseline and at the end of treatment for evaluation of cfDNA. Fill the Streck tube completely and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in accurate results. Ship within 24 hours of collection at ambient temperature overnight to:

Madeline Tenenbaum
450 Brookline Avenue, DA157
Boston, MA 02215
Ph: 617-632-2342
Fax: 617-632-3550
madeline_tenenbaum@dfci.harvard.edu

Email Madeline Tenenbaum with the sample information and tracking information the day before shipping specimens: madeline_tenenbaum@dfci.harvard.edu

Tube precautions:

- If samples cannot be shipped within 24 hours of collection, contact DFCI. DO NOT FREEZE OR REFRIDGERATE TUBES as this could result in cfDNA breakage. Blood collected in the Streck tube can be stored for 14 days between 6-37 degrees Celsius.
- Do not use tubes after expiration date.
- Fill the tube completely; overfilling or underfilling of tubes will result in an incorrect blood-to-additive ratio and may lead to incorrect analytical results.

Shipping Note: Streck tube samples are sent ambient. Frozen and ambient specimens obtained and shipped on the same day to Madeline Tenenbaum(e.g., Progression or Off Study Biopsy Specimens, Streck Tubes, and Circulating Tumor Cells) may be placed in a combination shipping box which contains separate compartments for frozen and ambient samples. If a combination shipping box is not available, two shipping boxes should be used.

Please refer to **Appendix H** for additional processing details specific to the laboratories at Dana-Farber Cancer Institute.

Procedures for Collecting and Shipping Optional Research Biopsy Tissue

Tissue specimens will be collected from recurrent or metastatic lesions using standard institutional procedures. The amount of tissue collected will follow the guidelines listed below:

Breast: A goal of 3-6 core biopsy specimens will be obtained using standard institutional guidelines for a diagnostic core biopsy of a breast mass.

Skin/chest wall: A goal of 1-2 5-mm punch biopsies will be obtained.

Lymph node: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Liver: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Lung: Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules will be performed on this protocol; unless if they are clinically indicated.

Bone: Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (i.e. skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 3-6 core biopsy specimens will be obtained using an 11-13 gauge needle.

Pleural Fluid: A goal of 500 cc of pleural fluid will be obtained with a standard thoracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable, and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.

Ascites fluid: A goal of 500 cc of ascites fluid will be obtained with a standard paracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable, and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.

Please note that the above are guidelines for the amount of tissue to be obtained, and are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure. If ascites or pleural fluid is to be used as the investigational biopsy specimen, consideration should be given to confirming the malignant nature of the ascites or pleural fluid prior to study entry.

If a patient is undergoing resection of a lesion for clinical reasons (i.e. wedge resection of a new lung lesion for confirmation of diagnosis or re-testing of hormone receptor or HER2 status; or, resection of a chest wall lesion; or, resection of a lymph node), then the patient may opt to have a portion of that tissue (roughly equivalent to the goal amount of tissue listed in the guidelines above, i.e. the equivalent of two 5-mm punch biopsies of the skin, or 3-6 18-gauge core biopsies) stored for research at the time of the procedure (provided that the tissue is processed as specified), in which case, the patient would not be required to undergo a separate research biopsy for entry into this protocol.

Half of the cores should be frozen in OCT and the other half should be placed in formalin and made into paraffin blocks.

Specimens will be shipped to the Clinical Research Coordinator, the frozen sample in OCT will be shipped on dry ice and the ones in formalin or paraffin will be shipped ambient, who will then deliver tissues to pathology lab:

Madeline Tenenbaum
450 Brookline Avenue, DA157
Boston, MA 02215
Ph: 617-632-2342
Fax: 617-632-3550
Madeline_tenenbaum@dfci.harvard.edu

Guidelines for Archival Tissue

Archival tissue from the most recent procedure is preferred, if available.

- 15 unstained slides and 1 H&E OR 1 block and 1 H&E
- Thickness of slides should be 4-5 μm

APPENDIX G: STUDY DRUG ORDER FORM

EXELIXIS™

PROTOCOL:

XL184 – IST-____

STUDY DRUG ORDER FORM

Investigator Name: _____
Contact Person: _____
Site Name &Address: _____
_____
_____
Phone/Fax: _____
Date Requested: _____
Date Required at Site: _____
Requested By: _____

DRUG ORDER REQUEST:

For Clinical Site Use Only:			For Exelixis Clinical Supplies Use Only:		
☐ Initial Supply ☐ Resupply			Exelixis Order #		
PRODUCT DESCRIPTION (30 Tablets per bottle)	REQUESTED QUANTITY	CURRENT INVENTORY	APPROVED QUANTITY	LOT NUMBER	PART NUMBER
XL184 20 mg Tab					
XL184 60 mg Tab					
Current # of Active Subjects					

To avoid any delays on shipment order processing, the "Requester" must complete all information requested on the form.

For Exelixis Clinical Supplies Use Only
Shipment Request Approved By:

Print Name / Signature		Date:	

SCAN THIS COMPLETED FORM TO EXELIXIS at clinical_supplies@exelixis.com.

APPENDIX H: STRECK COLLECTION AND PROCESSING INSTRUCTIONS – FOR OUTSIDE OF DFCI LAB USE ONLY

Cell-Free DNA BCT®

Streck

INSTRUCTIONS FOR USE

INTENDED USE

Cell-Free DNA BCT® is a direct draw whole blood collection tube intended for collection, stabilization and transportation of cell-free plasma DNA. This device also stabilizes and preserves cellular genomic DNA present in nucleated blood cells and circulating epithelial cells (tumor cells) found in whole blood. **This product has not been cleared by the U.S. Food and Drug Administration for In Vitro Diagnostic use. The product is For Research Use Only. Not for use in diagnostic procedures.**

SUMMARY AND PRINCIPLES

Accurate analysis of cf-DNA can be compromised by sample handling, shipping and processing, causing lysis of nucleated blood cells and subsequent release of cellular genomic DNA. Additionally, degradation of cf-DNA due to nuclease activity can be problematic.

The formaldehyde-free preservative reagent contained in Cell-Free DNA BCT®[1,2] stabilizes nucleated blood cells, preventing the release of cellular genomic DNA, and inhibits nuclease mediated degradation of cf-DNA, contributing to the overall stabilization of cf-DNA[3]. Samples collected in Cell-Free DNA BCT are stable for up to 14 days at temperatures between 6-37°C, allowing convenient sample collection, transport and storage[4].

The formaldehyde-free preservative reagent contained in Cell-Free DNA BCT stabilizes circulating epithelial cells (tumor cells) in whole blood for up to 4 days at temperatures between 15-30°C[5].

REAGENTS

Cell-Free DNA BCT contains the anticoagulant K_3EDTA and a cell preservative in a liquid medium.

PRECAUTIONS

1. **For Research Use Only. Not for use in diagnostic procedures.**
2. Do not freeze specimens collected in Cell-Free DNA BCT as breakage could result.
3. Do not use tubes after expiration date.
4. Do not use tubes for collection of materials to be injected into patients.
5. Product is intended for use as supplied. Do not dilute or add other components to Cell-Free DNA BCT.
6. Overfilling or underfilling of tubes will result in an incorrect blood-to-additive ratio and may lead to incorrect analytic results or poor product performance.
7. CAUTION
   a. Glass has the potential for breakage; precautionary measures should be taken during handling.
   b. All biological specimens and materials coming in contact with them are considered biohazards and should be treated as if capable of transmitting infection. Dispose of in accordance with federal, state and local regulations. Avoid contact with skin and mucous membranes.
   c. Product should be disposed with infectious medical waste.
   d. Remove and reinsert stopper by either gently rocking the stopper from side to side or by grasping with a simultaneous twisting and pulling action. A "thumb roll" procedure for stopper removal is NOT recommended as tube breakage and injury may result.
8. SDS can be obtained at www.streck.com or by calling 800-843-0912.

STORAGE AND STABILITY

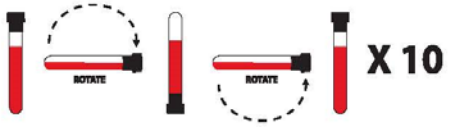
1. When stored at 18-30°C, unused Cell-Free DNA BCT is stable through expiration date.
2. Do not freeze unfilled Cell-Free DNA BCT. Proper insulation may be required for shipment during extreme temperature conditions.
3. Blood samples collected in Cell-Free DNA BCT for cf-DNA analysis are stable for 14 days when stored between 6-37°C.
4. Blood samples collected in Cell-Free DNA BCT for genomic DNA analysis are stable for 14 days when stored between 6-37°C.
5. Blood samples collected in Cell-Free DNA BCT for circulating epithelial cells (tumor cells) are stable for 4 days when stored between 15°-30°C.

INDICATIONS OF PRODUCT DETERIORATION

1. Cloudiness or precipitate visible in reagent of unused tube.
2. If indications of product deterioration occur, contact Streck Technical Services at 800-843-0912 or technicalservices@streck.com.

INSTRUCTIONS FOR USE

1. Collect specimen by venipuncture according to CLSI H3-A6[6].
   Prevention of Backflow - Since Cell-Free DNA BCT contains chemical additives, it is important to avoid possible backflow from the tube.
   To guard against backflow, observe the following precautions:
   a. Keep patient's arm in the downward position during the collection procedure.
   b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
   c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
2. Follow recommendations for order of draw outlined in CLSI H3-A6[6].
3. Fill tube completely.
4. Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180 degrees, and back per the figure below.



5. After collection, transport and store tubes within the recommended temperature range.
6. Perform extraction in accordance with instrument manufacturer's instructions. For optimal results, please follow the directions for cell-free plasma DNA and cellular genomic DNA extraction.

CELL-FREE PLASMA DNA AND CELLULAR GENOMIC DNA EXTRACTION

1. Extraction of cell-free plasma DNA and cellular genomic DNA can be accomplished using most commercially available kits.
2. For optimal results, include a Proteinase K treatment step (≥ 30 mAU/ml digest) at 60°C in the presence of chaotropic salts for 1 hour when extracting cell-free DNA and for 2 hours when extracting cellular genomic DNA.

Note:

a. Cell-Free DNA BCT does not dilute blood samples; therefore, no dilution factor correction is necessary to obtain absolute count values.
b. As in the case with most clinical laboratory specimens, hemolysis, icterus and lipemia may affect the results obtained on blood samples preserved with Cell-Free DNA BCT.

LIMITATIONS

1. Unused tubes to be stored between 18-30°C.
2. Samples drawn in other anticoagulants or preservatives may cause coagulation in Cell-Free DNA BCT.

REFERENCES

1. Das, K., Dumais, J., Basiaga, S., and Krzyzanowski, G., (2012). "Carbon-13 Nuclear Magnetic Resonance Analysis of Formaldehyde Free Preservatives." *Acta Histochemica*, 2013; 115: 481-486.
2. Das, K., Fernando, M.R., Basiaga, S., Wigginton, S., and Williams, T. (2013). "Effects of a Novel Cell Stabilizing Reagent on DNA Amplification by PCR as Compared to Traditional Stabilizing Reagents." *Acta Histochemica*, 2014; 116: 55-60.
3. Norton, S.E., Lechner, J.M., Williams, T., and Fernando, M.R., (2013). "A Stabilizing Reagent Prevents Cell-free DNA Contamination by Cellular DNA in Plasma during Blood Sample Storage and Shipping as Determined by Digital PCR." *Clinical Biochemistry*, 2013; 46: 1561-1565.
4. Norton, S.E., Luna, K.K., Lechner, J.M., Qin, J., and Fernando, M.R., (2013). "A New Blood Collection Device Minimizes Cellular DNA Release During Sample Storage & Shipping When Compared to a Standard Device." *Journal of Clinical Laboratory Analysis*, 2013; 27: 305-311.
5. Qin, J., Alt, J.R., Hunsley, B., Williams, T., and Fernando, M.R. (2013). "Stabilization of Circulating Tumor Cells in Blood Using a Collection Device with a Preservative Reagent." *Cancer Cell International*, 2014, 14:23.
6. Clinical and Laboratory Standards Institute. H3-A6, *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard-Sixth Edition.*

ORDERING INFORMATION

Please call our Customer Service Department toll free 800-228-6090 for assistance. Additional information can be found online at www.streck.com.

GLOSSARY OF HARMONIZED SYMBOLS

EC REP Authorized Representative in the European Community	LOT Batch Code	Biological Risk	REF Catalog Number	Use By
IVD In Vitro Diagnostic Medical Device	Manufacturer	Consult Instructions For Use	Temperature Limitation	Do Not Re-use
Glossary of symbols may contain symbols not used in the labeling of this product.				

See www.streck.com/patents for patents that may be applicable to this product.

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350547-6
2014-04

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**14-359**
Protocol Name:	**A Phase II Study of cabozantinib alone or in combination with trastuzumab in breast cancer patients with brain metastases**
DFCI Site PI:	Sara Tolaney, MD, MPH
DFCI Research Nurse:	Peg Haldoupis, RN; Liz Kasparian, RN; Mary O'Driscoll, RN; Kathy Roche, RN; Myra St. Amand, 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	It is estimated that approximately 10-15% of women with metastatic breast cancer will eventually develop brain metastases. Recent data suggests that anti-angiogenic therapy can be safely given to patients with brain metastases and clinical activity has been noted. Evidence from studies suggests that **cabozantinib** has anti-angiogenic activity, CNS penetration, activity in breast cancer and could be efficacious in the treatment of brain metastases from breast cancer. In this study, participants with HER2-positive will also be treated with **trastuzumab** (humanized anti-HER2 antibody). **Study Design** – Section 1.1; **Study Rationale** – Section 2.6; **A cycle is 21 days** – Section 1.1
Dose Calc.	• **Cabozantinib** is fixed dosing in mg; no calculation is required – Section 5.4.1 • **Trastuzumab** is dosed in mg/kg – Section 5.4.2
Study Drug Administration	**Cabozantinib** – Sections 5.1 and 5.4.1 • Pre-treatment criteria – Section 5.2 • Oral, taken once per day each morning with a full glass of water (minimum 8oz/240mL) – Section 5.4.1 • Must fast 2 hours before and 1 hour after dose; Tablets must be swallowed whole & not chewed – Section 5.4.1 • Missed doses may taken up to 12 hours after scheduled dosing time – Section 5.4.1 • Vomited doses are not re-taken – Section 5.4.1 • Grapefruit and Seville oranges must be avoided while on study – Section 5.6.1 **Trastuzumab** – Section 5.1 and 5.4.2 • IV, administered on Day 1 of each cycle – Section 5.4.2 • A loading may be required for some participants. Please see Section 5.4.2 for guidelines on loading doses and rate(s) of infusion. • Infusion reactions – see Section 7.2 for management and required observation periods post-reaction.
Dose Modifications & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are in *Sections 6* (**cabozantinib**) and *Section 7* (**trastuzumab**) • This protocol uses NCI CTCAE criteria, version 4.0 – Section 6 • The definition of a DLT (for the cabozantinib + trastuzumab cohort) is in Section 5.3 • Clinical experience of cabozantinib is in Section 2.3 • Safety profile of trastuzumab is in Section 2.4.2
Con Meds	*Concomitant Therapy* Guidelines are in Sections 5.5 and 5.6 • Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods
Required Data	*Study Calendar and Assessment Required data* are outlined in Sections 9 and 10 • Please review the study calendar in Section 10
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please also DOCUMENT any required observation periods (i.e. if an infusion reaction occurs), any additional vital signs, routes of administration.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Herceptin safely and effectively. See full prescribing information for Herceptin.

HERCEPTIN® (trastuzumab) for injection, for intravenous use
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: Herceptin can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1)	04/2017
Warnings and Precautions (5.3)	03/2016

----------INDICATIONS AND USAGE----------

Herceptin is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin (1, 2.1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution
- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

----------ADVERSE REACTIONS----------

Adjuvant Breast Cancer

- Most common adverse reactions (≥ 5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6.1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥ 10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Herceptin (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

1 INDICATIONS AND USAGE
- 1.1 Adjuvant Breast Cancer
- 1.2 Metastatic Breast Cancer
- 1.3 Metastatic Gastric Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Patient Selection
- 2.2 Recommended Doses and Schedules
- 2.3 Important Dosing Considerations
- 2.4 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Cardiomyopathy
- 5.2 Infusion Reactions
- 5.3 Embryo-Fetal Toxicity
- 5.4 Pulmonary Toxicity
- 5.5 Exacerbation of Chemotherapy-Induced Neutropenia

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Adjuvant Breast Cancer
- 14.2 Metastatic Breast Cancer
- 14.3 Metastatic Gastric Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Stability and Storage

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].*

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)].*

Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)].*

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Herceptin with other drugs.**
- **Do not substitute Herceptin (trastuzumab) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer

- Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer

- Administer Herceptin at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Herceptin maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[See Boxed Warning, Warnings and Precautions (5.2)]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Herceptin for severe or life-threatening infusion reactions.

Cardiomyopathy

[See Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Herceptin may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%.

Permanently discontinue Herceptin for a persistent (> 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not ado-trastuzumab emtansine.

<u>420 mg Multiple-dose vial</u>

Reconstitution

Reconstitute each 420 mg vial of Herceptin with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab that delivers 20 mL (420 mg trastuzumab). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Herceptin. The stream of diluent should be directed into the lyophilized cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted Herceptin in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused Herceptin after 28 days. If Herceptin is reconstituted with SWFI without preservative, use immediately and discard any unused portion. **Do not freeze.**

Dilution

- Determine the dose (mg) of Herceptin *[see Dosage and Administration (2.2)]*. Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. **Do not freeze.**

150 mg Single-dose vial

Reconstitution

Reconstitute each 150 mg vial of Herceptin with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab).

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized 150 mg Herceptin, directing the diluent stream into the lyophilized cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE**.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused Herceptin after 24 hours. **Do not freeze.**

Dilution

- Determine the dose (mg) of Herceptin *[see Dosage and Administration (2.1)]*.
- Calculate the volume of the 21 mg/mL reconstituted Herceptin solution needed.
- Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. **Do not freeze**.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 150 mg lyophilized powder in a single-dose vial
- For injection: 420 mg lyophilized powder in a multiple-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

Withhold Herceptin for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.3)]*. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.3)]*
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.

In Study 1, 15% (158/1031) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH arm. In Study 3 (one-year Herceptin treatment), the number of patients who discontinued Herceptin due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented etiology, and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of congestive heart failure (CHF) is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Table 1
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence of CHF	
Study	Regimen	Herceptin	Control
1 & 2[a]	AC[b]→Paclitaxel+Herceptin	3.2% (64/2000)[c]	1.3% (21/1655)
3[d]	Chemo → Herceptin	2% (30/1678)	0.3% (5/1708)
4	AC[b]→Docetaxel+Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+Herceptin	0.4% (4/1056)	0.3% (3/1050)

[a] Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC→TH arm.
[b] Anthracycline (doxorubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.
[d] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year Herceptin arm.

In Study 3 (one-year Herceptin treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2
Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I–IV		NYHA III–IV	
Study	Event	Herceptin	Control	Herceptin	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a] Congestive heart failure or significant asymptomatic decrease in LVEF.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the Herceptin containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia *[see Adverse Reactions (6.1)]*.

In post-marketing reports, serious and fatal infusion reactions have been reported. Severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications.

5.3 Embryo-Fetal Toxicity

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Herceptin. Advise pregnant women and females of reproductive potential that exposure to Herceptin during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Herceptin *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)]*.

5.4 Pulmonary Toxicity

Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see Warnings and Precautions (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.5 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3–4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received Herceptin and those who did not *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Exacerbation of Chemotherapy-Induced Neutropenia *[see Warnings and Precautions (5.5)]*

The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in

left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.3)]*.

In the metastatic gastric cancer setting, the most common adverse reactions (≥ 10%) that were increased (≥ 5% difference) in the Herceptin arm as compared to the chemotherapy alone arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Breast Cancer Studies

The data below reflect exposure to one-year Herceptin therapy across three randomized, open-label studies, Studies 1, 2, and 3, with (n = 3678) or without (n = 3363) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in the observation and one-year Herceptin arms of Study 3 at a median duration of follow-up of 12.6 months in the Herceptin arm, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3
Adverse Reactions for Study 3[a], All Grades[b]

Adverse Reaction	One Year Herceptin (n = 1678)	Observation (n = 1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[c]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritus	40 (2%)	10 (0.6%)

Table 3 (cont'd)
Adverse Reactions for Study 3[a], All Grades[b]

Adverse Reaction	One Year Herceptin (n = 1678)	Observation (n = 1708)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Asthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

[a] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.
[b] The incidence of Grade 3 or higher adverse reactions was <1% in both arms for each listed term.
[c] Higher level grouping term.

In Study 3, a comparison of 3-weekly Herceptin treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year Herceptin treatment arm (8.1% versus 4.6% in the one-year Herceptin treatment arm). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year Herceptin treatment arm (20.4%) compared with the one-year Herceptin treatment arm (16.3%).

The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received Herceptin; the median treatment duration was 51 weeks. The median age was 49 years (range: 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs. 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs. 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7% vs. 2.7%), and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, and sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes (11.5% vs. 6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these events were Grade 2 in severity.

Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n = 1056].

The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm.

Metastatic Breast Cancer Studies

The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of chemotherapy with (n = 235) or without (n = 234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n = 222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 5 and 6.

Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian, and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28–86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 31% and 16%, respectively.

Table 4

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Body as a Whole					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%

Table 4 (cont'd)

Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The data below are based on the exposure of 294 patients to Herceptin in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the Herceptin plus chemotherapy arm, the initial dose of Herceptin 8 mg/kg was administered on Day 1 (prior to

chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1–14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21-day cycles. Median duration of Herceptin treatment was 21 weeks; median number of Herceptin infusions administered was eight.

Table 5

Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1% between Arms) and Higher Incidence in Herceptin Arm

	Herceptin + FC (N = 294) N (%)		FC (N = 290) N (%)	
Body System/Adverse Event	All Grades	Grades 3/4	All Grades	Grades 3/4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	15 (5)	—	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤ 1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)
Chills	23 (8)	1 (≤ 1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections and Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal and Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience.

Cardiomyopathy

Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized patients with post-AC LVEF evaluation were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving one-year Herceptin monotherapy compared to observation in Study 3 (see Table 6, Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Table 6[a]

Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF < 50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF < 50%	≥ 10% decrease	≥ 16% decrease	< 20% and ≥ 10%	≥ 20%
Studies 1 & 2[b,c]					
AC→TH (n = 1856)	23.1% (428)	18.5% (344)	11.2% (208)	37.9% (703)	8.9% (166)
AC→T (n = 1170)	11.7% (137)	7.0% (82)	3.0% (35)	22.1% (259)	3.4% (40)
Study 3[d]					
Herceptin (n = 1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n = 1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4[e]					
TCH (n = 1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n = 1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n = 1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

[b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

[c] Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC→TH arm.

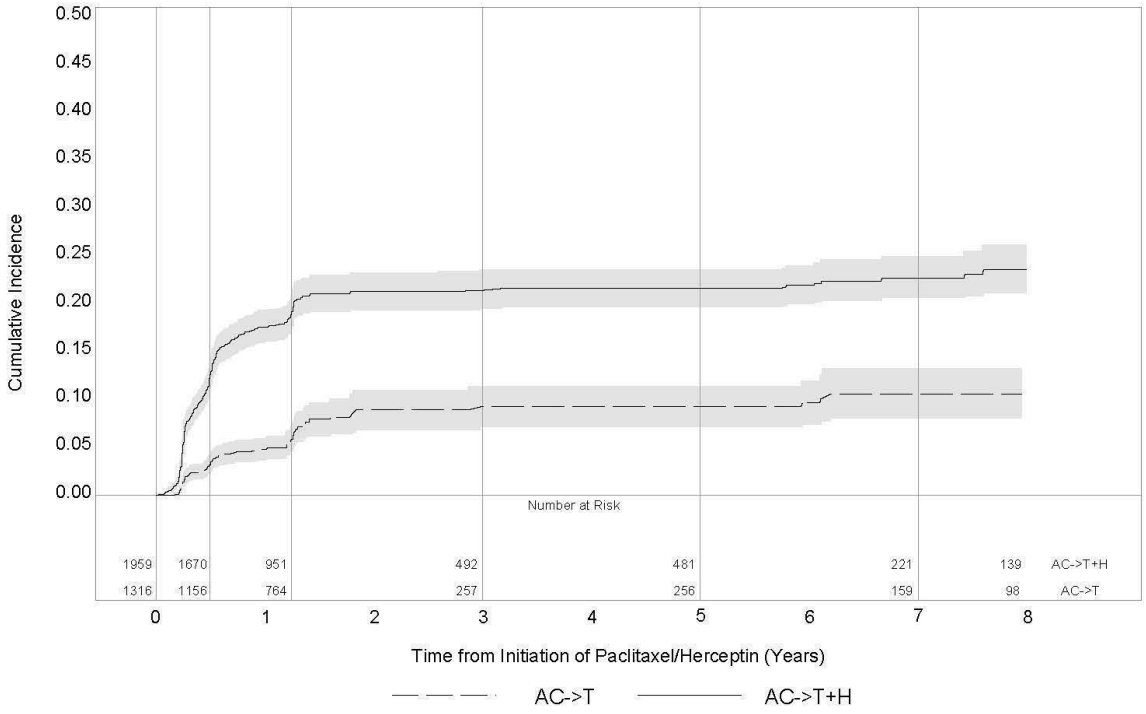
[d] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

[e] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

409

Figure 1

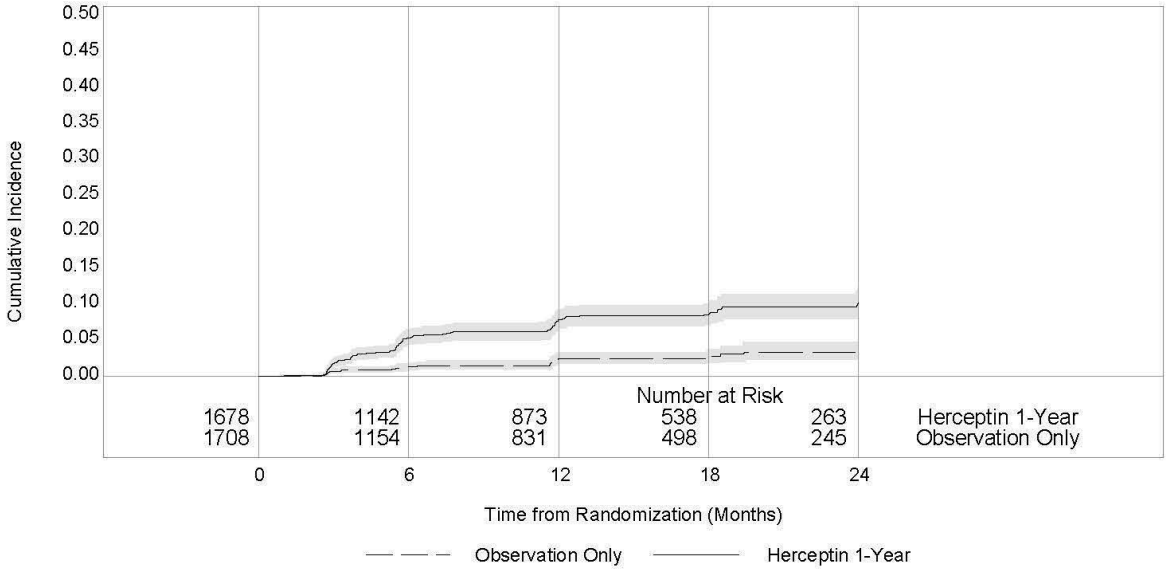
Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2

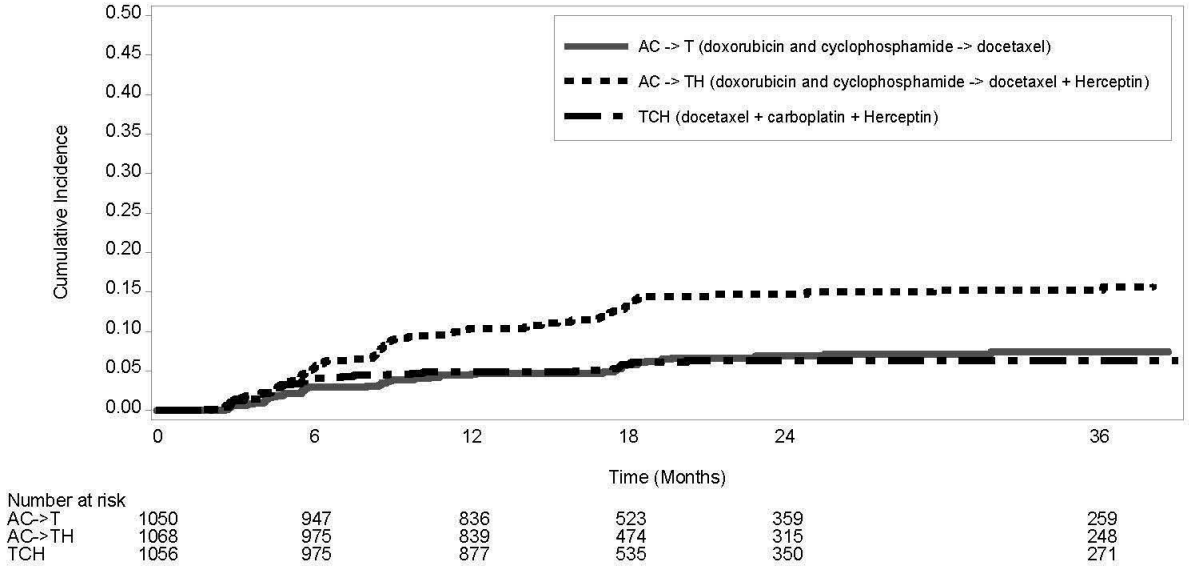
Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

Figure 3

Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials, the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines.

In Study 7, 5.0% of patients in the Herceptin plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥10% absolute decrease in LVEF from pretreatment values.

Infusion Reactions

During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusion reactions was required in < 1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusion reactions occurred in 21% and 35% of patients, and were severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

Anemia

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2−5 anemia (12.3% vs. 6.7% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer), on the Herceptin containing arm as compared to the chemotherapy alone arm, the overall incidence of anemia was 28% compared to 21% and of NCI-CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

Neutropenia

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4−5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2−5 neutropenia (6.4% vs. 4.3% [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the Herceptin containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

Infection

The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2−5 infection/febrile neutropenia (24.3% vs. 13.4% [Study 1]) and of selected Grade 3−5 infection/febrile neutropenia (2.9% vs. 1.4%) [Study 2]) were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3−4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Pulmonary Toxicity

Adjuvant Breast Cancer

Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14.3% vs. 5.4% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4% vs. 0.9% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 11.8% vs. 4.6% [Study 1]; NCI-CTC Grade 2–5: 2.4% vs. 0.2% [Study 2]).

Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

In Study 3, there were 4 cases of interstitial pneumonitis in the one-year Herceptin treatment arm compared to none in the observation arm at a median follow-up duration of 12.6 months.

Metastatic Breast Cancer

Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions (5.4)*.

Thrombosis/Embolism

In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

Diarrhea

Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (2.2% vs. 0% [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3; one-year Herceptin treatment at 12.6 months median duration of follow-up]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer.

Renal Toxicity

In Study 7 (metastatic gastric cancer) on the Herceptin-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the Herceptin-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the Herceptin-containing arm and 0.3% on the chemotherapy only arm.

In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous

glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Herceptin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infusion reaction *[see Warnings and Precautions (5.2)]*
- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Warnings and Precautions (5.3)]*
- Glomerulopathy *[see Adverse Reactions (6.1)]*
- Immune thrombocytopenia

7 DRUG INTERACTIONS

Patients who receive anthracycline after stopping Herceptin may be at increased risk of cardiac dysfunction because of trastuzumab's long washout period based on population PK analysis *[see Clinical Pharmacology (12.3)]*. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry and Pharmacovigilance Program

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Herceptin during pregnancy. Encourage women who receive Herceptin during pregnancy or within 7 months prior to conception to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 or visiting http://www.motherpregnancyregistry.com/.

In addition, there is a pregnancy pharmacovigilance program for Herceptin. If Herceptin is administered during pregnancy, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, health care providers and patients should immediately report Herceptin exposure to Genentech at 1-888-835-2555.

Risk Summary

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Data]*. Apprise the patient of the potential risks to a fetus. There are clinical

considerations if Herceptin is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of Herceptin *[see Clinical Considerations]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received Herceptin during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after amniotic index improved and oligohydramnios recurred.

Animal Data

In studies where trastuzumab was administered to pregnant Cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity *[see Data]*. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Herceptin treatment and any potential adverse effects on the breastfed child from Herceptin or from the underlying maternal condition. This consideration should also take into account the trastuzumab wash out period of 7 months *[see Clinical Pharmacology (12.3)]*.

Data

In lactating Cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of Herceptin). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of Herceptin.

Contraception

Females

Herceptin can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Herceptin and for 7 months following the last dose of Herceptin *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of Herceptin in pediatric patients have not been established.

8.5 Geriatric Use

Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients < 65 years of age for metastatic disease and adjuvant treatment.

In Study 7 (metastatic gastric cancer), of the 294 patients treated with Herceptin, 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested.

11 DESCRIPTION

Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin (trastuzumab) is a sterile, white to pale yellow, preservative-free lyophilized powder for Injection, for intravenous administration.

Each multiple-dose vial of Herceptin delivers 420 mg trastuzumab, 381.8 mg α,α-trehalose dihydrate, 9.5 mg L-histidine HCl monohydrate, 6.1 mg L-histidine, and 1.7 mg polysorbate 20. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab at a pH of approximately 6. If Herceptin is reconstituted with SWFI without preservative, the reconstituted solution is considered single-dose.

Each single-dose vial of Herceptin delivers 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20. Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab was evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous Herceptin. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of Herceptin, the average steady-state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first Herceptin cycle and at steady state exposure are described in Tables 7 and 8, respectively.

Population PK based simulations indicate that following discontinuation of Herceptin, concentrations in at least 95% of breast cancer and MGC patients will decrease to approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months *[see Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1, 8.3)]*.

Table 7

Population Predicted Cycle 1 PK Exposures (Median with 5^{th} – 95^{th} Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	MGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Table 8

Population Predicted Steady State PK Exposures (Median with 5th - 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	$C_{min,ss}$[a] (µg/mL)	$C_{max,ss}$[b] (µg/mL)	$AUC_{ss,\ 0\text{-}21\ days}$ (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	MGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

[a] Steady-state trough serum concentration of trastuzumab
[b] Maximum steady-state serum concentration of trastuzumab

Specific Populations

Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (< 65 (n = 1294); ≥ 65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

Drug Interaction Studies

There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and concomitant medications used in clinical trials have not been observed.

Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6-α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

Docetaxel and carboplatin: When Herceptin was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab were altered.

Cisplatin and capecitabine: In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Herceptin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Herceptin has not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays at concentrations of up to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.

A fertility study was conducted in female Cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

The safety and efficacy of Herceptin in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year Herceptin treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Studies 1 and 2

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mm Hg or systolic > 200 mm Hg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) alone or paclitaxel plus Herceptin (AC→paclitaxel + Herceptin). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Herceptin was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Herceptin treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline *[see Dosage and Administration (2.3)]*. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death. The secondary endpoint was overall survival (OS).

A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2.0 years in the AC→paclitaxel + Herceptin arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC→paclitaxel + Herceptin arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of 49 years (range, 22–80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy evaluable population, after 8.3 years of median follow-up in the AC→paclitaxel + Herceptin arm.

Study 3

In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart failure or LVEF < 55%, uncontrolled arrhythmias, angina requiring medication, clinically significant

valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Study 3 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of Herceptin treatment or two years of Herceptin treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Herceptin was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

A protocol specified interim efficacy analysis comparing one-year Herceptin treatment to observation was performed at a median follow-up duration of 12.6 months in the Herceptin arm and formed the basis for the definitive DFS results from this study. Among the 3386 patients randomized to the observation (n = 1693) and Herceptin one-year (n = 1693) treatment arms, the median age was 49 years (range 21–80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER– and PgR–, and 47% (512) were ER and/or PgR+ and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2–3, or age < 35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

After the definitive DFS results comparing observation to one-year Herceptin treatment were disclosed, a prospectively planned analysis that included comparison of one year versus two years of Herceptin treatment at a median follow-up duration of 8 years was performed. Based on this analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for one year [Hazard Ratios of two-years Herceptin versus one-year Herceptin treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI: 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

Study 4

In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or N2, or known N3 or M1 breast cancer were not eligible.

Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus Herceptin (AC-TH), or docetaxel and carboplatin plus Herceptin (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered every 3 weeks for four cycles; docetaxel 100 mg/m^2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m^2 and carboplatin (at a target AUC of 6 mg/mL/min as a 30- to 60-minute infusion) were administered every 3 weeks for six cycles. Herceptin was administered weekly (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6% ≥ 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to randomization, all patients underwent primary surgery for breast cancer.

The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC→TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC→TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients > 65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC→TH], the survival rate was estimated to be 86.9% in the AC→TH arm and 79.4% in the AC→T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

Table 9
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies 1 + 2[a]				
AC→TH (n = 1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) p< 0.0001[e]	289[c]	0.64[c,d] (0.55, 0.74) p< 0.0001[e]
AC→T (n = 1880)[b] (n = 2032)[c]	261[b]		418[c]	
Study 3[f]				
Chemo→ Herceptin (n = 1693)	127	0.54 (0.44, 0.67) p< 0.0001[g]	31	0.75 p = NS[h]
Chemo→ Observation (n = 1693)	219		40	
Study 4[i]				
TCH (n = 1075)	134	0.67 (0.54 – 0.84) p=0.0006[e,j]	56	
AC→TH (n = 1074)	121	0.60 (0.48 – 0.76) p< 0.0001[e,i]	49	
AC→T (n = 1073)	180		80	

CI = confidence interval.

[a] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH).

[b] Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC→TH arm.

[c] Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC→TH arm).

[d] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[e] stratified log-rank test.

[f] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year Herceptin treatment arm.

[g] log-rank test.

[h] NS = non-significant.

[i] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

[j] A two-sided alpha level of 0.025 for each comparison.

865

Figure 4

Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

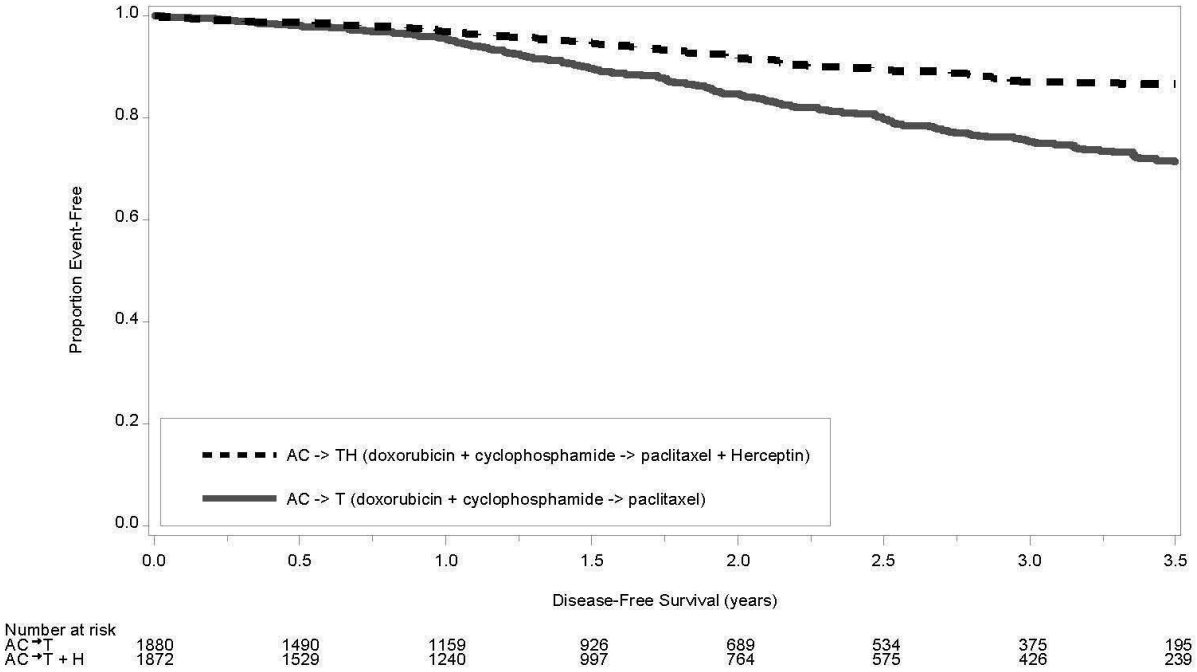
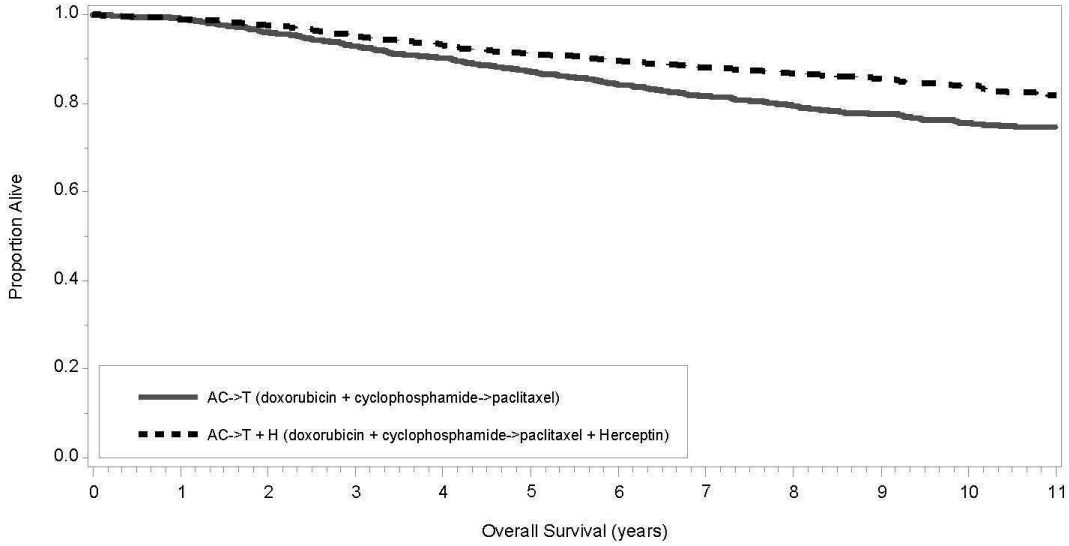


Figure 5

Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

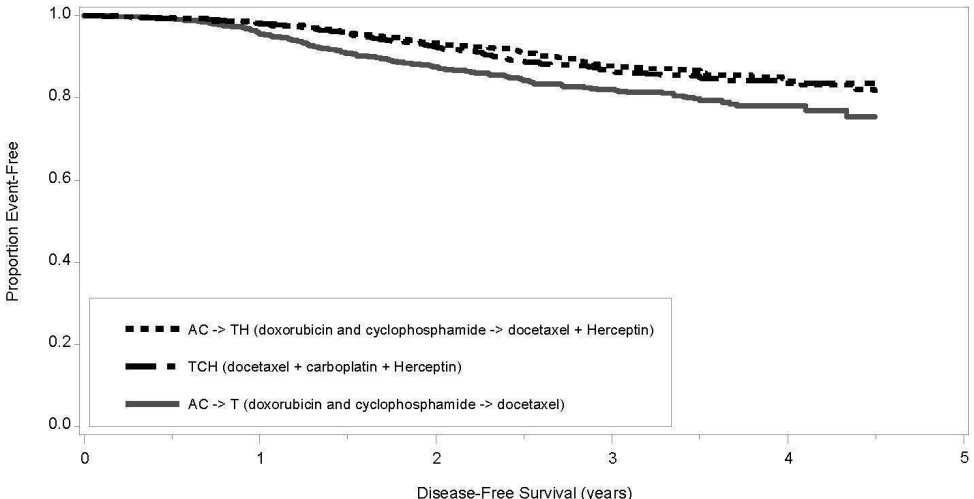


Number at risk

AC->T	2032	1961	1883	1806	1732	1643	1538	1377	979	630	399	151
AC->T + H	2031	1992	1957	1897	1843	1787	1714	1533	1127	787	485	159

Figure 6

Duration of Disease-Free Survival in Patients with
Adjuvant Treatment of Breast Cancer (Study 4)



Number at risk

AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and Herceptin; TH=docetaxel and Herceptin.
Kaplan-Meier estimates are shown.

Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of

the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.

Table 10
Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

	Study 2		Study 3[c]	
HER2 Assay Result[a]	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (–)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)
IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299[b]	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

[a] IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.
[b] All cases in this category in Study 3 were IHC 2+.
[c] Median follow-up duration of 12.6 months in the one-year Herceptin treatment arm.

14.2 Metastatic Breast Cancer

The safety and efficacy of Herceptin in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Previously Untreated Metastatic Breast Cancer (Study 5)

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses of Herceptin at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to

receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee, the patients randomized to Herceptin and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response as compared with patients randomized to chemotherapy alone. Patients randomized to Herceptin and chemotherapy also had a longer median survival (see Table 11). These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received Herceptin plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

Table 11
Study 5: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	Herceptin + All Chemo-therapy (n = 235)	All Chemo-therapy (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] $\chi 2$-test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 12).

Table 12
Treatment Effects in Study 5 as a
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk[b] for Time to Disease Progression (95% CI)	Relative Risk[b] for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)[a]	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (–)[a]	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)
FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (–)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (–)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

[a] FISH testing results were available for 451 of the 469 patients enrolled on study.
[b] The relative risk represents the risk of progression or death in the Herceptin plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 6)

Herceptin was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of Herceptin at 2 mg/kg IV.

The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

14.3 Metastatic Gastric Cancer

The safety and efficacy of Herceptin in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to Herceptin in combination with cisplatin and a fluoropyrimidine (FC+H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the Herceptin-containing arm, Herceptin was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m^2 Day 1 every 3 weeks for 6 cycles as a 2 hour IV

infusion. On both study arms, capecitabine was administered at 1000 mg/m^2 dose orally twice daily (total daily dose 2000 mg/m^2) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m^2/day from Day 1 through Day 5 every three weeks for 6 cycles.

The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13 and Figure 7.

Table 13

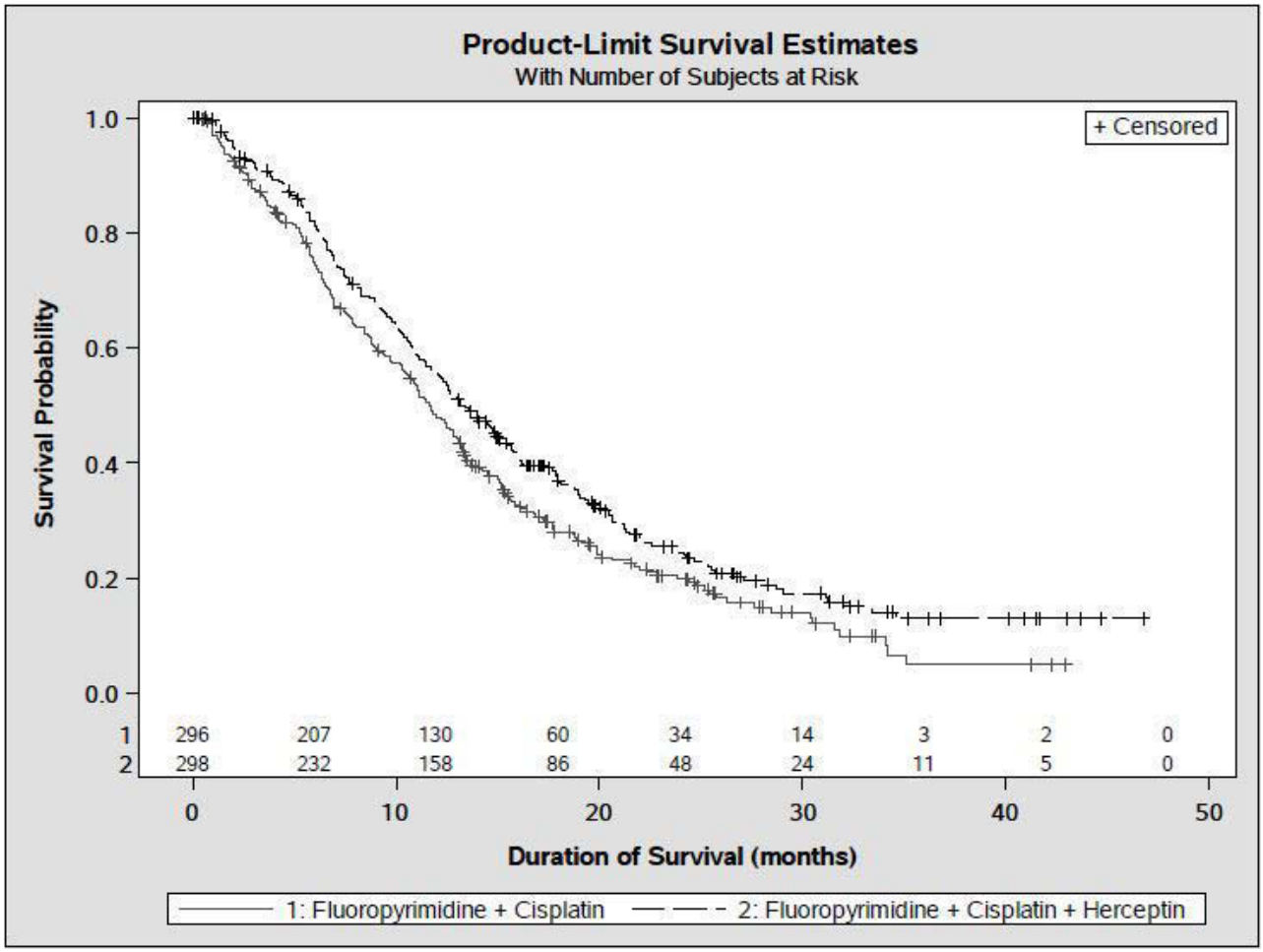
Study 7: Overall Survival in ITT Population

	FC Arm N = 296	FC + H Arm N = 298
Definitive (Second Interim) Overall Survival		
No. Deaths (%)	184 (62.2%)	167 (56.0%)
Median	11.0	13.5
95% CI (mos.)	(9.4, 12.5)	(11.7, 15.7)
Hazard Ratio	0.73	
95% CI	(0.60, 0.91)	
p-value*, two-sided	0.0038	
Updated Overall Survival		
No. Deaths (%)	227 (76.7%)	221 (74.2%)
Median	11.7	13.1
95% CI (mos.)	(10.3, 13.0)	(11.9, 15.1)
Hazard Ratio	0.80	
95% CI	(0.67, 0.97)	

* Comparing with the nominal significance level of 0.0193.

Figure 7

Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14
Exploratory Analyses by HER2 Status Using Updated Overall Survival Results

	FC (N = 296)[a]	FC+H (N = 298)[b]
FISH+ / IHC 0, 1+ subgroup (N=133)		
No. Deaths / n (%)	57/71 (80%)	56/62 (90%)
Median OS Duration (mos.)	8.8	8.3
95% CI (mos.)	(6.4, 11.7)	(6.2, 10.7)
Hazard ratio (95% CI)	1.33 (0.92, 1.92)	
FISH+ / IHC2+ subgroup (N=160)		
No. Deaths / n (%)	65/80 (81%)	64/80 (80%)
Median OS Duration (mos.)	10.8	12.3
95% CI (mos.)	(6.8, 12.8)	(9.5, 15.7)
Hazard ratio (95% CI)	0.78 (0.55, 1.10)	
FISH+ or FISH- / IHC3+[c] subgroup (N=294)		
No. Deaths / n (%)	104/143 (73%)	96/151 (64%)
Median OS Duration (mos.)	13.2	18.0
95% CI (mos.)	(11.5, 15.2)	(15.5, 21.2)
Hazard ratio (95% CI)	0.66 (0.50, 0.87)	

[a] Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

[b] Five patients on the Herceptin-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

[c] Includes 6 patients on chemotherapy arm, 10 patients on Herceptin arm with FISH–, IHC3+ and 8 patients on chemotherapy arm, 8 patients on Herceptin arm with FISH status unknown, IHC 3+.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

420 mg Multiple-dose vial

Herceptin (trastuzumab) for Injection 420 mg/vial is supplied in a multiple-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial of Herceptin and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

NDC 50242-333-01.

150 mg Single-dose vial

Herceptin (trastuzumab) for Injection 150 mg/vial is supplied in a single-dose vial as a lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial of Herceptin.

NDC 50242-132-01.

16.2 Storage

Store Herceptin vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face,

palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Boxed Warning: Cardiomyopathy]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that Herceptin exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise women who are exposed to Herceptin during pregnancy or who become pregnant within 7 months following the last dose of Herceptin that there is a pregnancy exposure registry and a pregnancy pharmacovigilance program that monitor pregnancy outcomes. Encourage these patients to enroll in the MotHER Pregnancy Registry and report their pregnancy to Genentech *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Herceptin *[see Use in Specific Populations (8.3)]*.

HERCEPTIN® [trastuzumab]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.1048

Genentech
A Member of the Roche Group

May 2017

ANNOUNCEMENT – HERCEPTIN® VIAL CHANGE

Dear Pharmacist:

We want to make you aware of an upcoming change to Herceptin (trastuzumab). Recently, the FDA approved a revised USPI for Herceptin (dated 04/2017) that lists a new 150mg singe-dose configuration along with additional label changes to meet current FDA guidance. The new 150mg single-dose vial configuration for Herceptin will be introduced on May 30, 2017.

Important information for you to know:

- All customers will be asked to transition to the 150mg single-dose vial once available for order on May 30th. After July 7, 2017, Genentech will only ship 150mg vials to distributors and will discontinue shipping the 440mg multiple-dose vial to distributors.
- The National Drug Code (NDC) for the Herceptin 150mg vial is: 50242-132-01.
- After July 7th, you may continue using any 440mg vials in your inventory until the expiration date noted on the vial when stored in conditions recommended in the USPI.
- All payers, pharmacies and distributors should confirm that the current NDC for the 440mg multiple-use vial [NDC 50242-134-68] remains active within all systems, through product expiration date, in order to ensure this medicine remains available to providers and patients.
- The Herceptin Wholesale Acquisition Cost (WAC) per milligram does not change with the new 150mg vial introduction.
- Authorized Herceptin distributors do not change. A complete listing of distributors can be found on https://www.genentech-access.com/hcp/brands/herceptin/learn-about-our-services/product-distribution.html

Decisions on how we manufacture and package our medicines are taken very seriously and all of our medicines, including all configurations of Herceptin, are packaged to meet FDA regulations and specifications. If you have any questions, please contact your Genentech Clinical Oncology Specialist or call the Genentech Customer Service Department at 1-800-551-2231, Monday through Friday, 6:00AM to 5:00PM PST.

Sincerely,

Cindy Perettie
Vice President, HER2 Franchise
Genentech USA, Inc.

HPK/102416/0066

Indications

Adjuvant Breast Cancer
Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:
- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy
- Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin

*High-risk is defined as ER/PR positive with one of the following features: tumor size >2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer
Herceptin is indicated:
- In combination with paclitaxel for the first line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease
- Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin

Metastatic Gastric Cancer
Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.
Select patients for therapy based on an FDA-approved companion diagnostic for Herceptin

Boxed WARNINGS and Additional Important Safety Information

- **Herceptin administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Herceptin with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant trial, one patient who developed CHF died of cardiomyopathy**
- **Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and withhold Herceptin in patients with metastatic disease for clinically significant decrease in left ventricular function**
- **Herceptin administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of Herceptin administration. Interrupt Herceptin infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome**
- **Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- Exacerbation of chemotherapy-induced neutropenia has also occurred
- The most common adverse reactions associated with Herceptin in breast cancer were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
- The most common adverse reactions associated with Herceptin in metastatic gastric cancer were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see the accompanying full Prescribing Information, including **Boxed WARNINGS**.

STUDY PHARMACY MANUAL

PROTOCOL NUMBER: IST-_____

XL184-Investigator Sponsored Trial (IST)

Investigational Product Main Distributor:	Exelixis, Inc. 210 East Grand Avenue South San Francisco, CA 94080
Study Drug:	Cabozantinib (XL184) Tablets
IND Number:	72,596
Date:	21-Nov-2017
Version Number:	3.0

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 upon request following regulatory approval and site activation by Exelixis.

XL184-IST PHARMACY MANUAL

Table of Contents

1 SITE PERSONNEL RESPONSIBILITIES 4

2 STUDY DESCRIPTION....4

3 INVESTIGATIONAL PRODUCT DESCRIPTION AND PACKAGING 4

3.1 Cabozantinib (XL184) Description....4
3.2 Cabozantinib (XL184) Packaging 5

4 STORAGE AND HANDLING 5

5 DRUG SHIPMENTS....5

5.1 Initial and Resupply Shipments 5
5.2 Shipment Requests and Timelines....5
5.3 Drug Expiry Date and Notification 6
5.4 Drug Receipt and Confirmation 6

6 INVESTIGATIONAL PRODUCT ADMINISTRATION 7

6.1 Dispensation and Administration 7
6.1.1 Cabozantinib Dispensation 7
6.1.2 Cabozantinib Administration 7
6.2 Instructions on Dose Reduction and/or Hold 7
6.3 Subject Dosing Instructions....7

7 RECORD KEEPING……7

8 INVESTIGATIONAL PRODUCT ACCOUNTABILITY PROCEDURES 8

9 INVESTIGATIONAL PRODUCT DISPOSITION 8

10 PHARMACY MANUAL HISTORY .... ……....8

ATTACHMENT 1.0 SAMPLE OF DRUG REQUEST FORM……...10

ATTACHMENT 2.0 INSTRUCTIONS FOR WRITING IN STUDY IDENTIFIER…11

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 study protocol for a detailed description of the study.

3 INVESTIGATIONAL PRODUCT DESCRIPTION AND PACKAGING

Exelixis will provide approved investigative sites with adequate supplies of labeled IP (refer to Attachment 2.0 for example label).

3.1 Cabozantinib (XL184) Description

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.

3.2 Cabozantinib (XL184) Packaging

IP will be provided in 60cc HDPE white bottles containing 30 tablets each. Each bottle will be printed with a unique 7-digit bottle number and a lot number for tracking purposes. The IP label will have a blank line under the drug type and drug name where the site staff will need to write in the specific IST Study Identifier (see Attachment 2.0).

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. Please contact Exelixis Clinical Supplies at Clinical_Supplies@exelixis.com immediately in case of any temperature excursions outside the accepted range. All affected IP will need to be quarantined until further notification.

Refer to the Cabozantinib Material Safety Data Sheet (MSDS) for additional handling information if required.

Subjects need to be instructed to:

- 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 DRUG SHIPMENTS

5.1 Initial and Re-supply Shipments

After IST site activation, the site is required to submit the completed Initial Exelixis Study Drug Shipment Request Form (see Attachment 1.0) by email to Clinical_Supplies@Exelixis.com. Subsequent re-supply shipments of IP will be made by following the same process outlined above.

All Exelixis Study Drug Shipment Request Forms must be fully completed (see below) to avoid any delays:

- Complete Section 1.0: Site Information
    - Investigator Name

- Contact Name
- Site Name and Address
- Phone/Fax
- Date Requested/Required
- Requested By

- Complete Section 2.0: Drug Request
  - Check the appropriate box for “Initial” or “Resupply”
  - Requested Quantity and Current Inventory
  - Current # of active patients and their current dose

Note: Allow 3-5 business days for processing and delivery of shipments.

5.2 Shipment Requests and Timelines

General drug shipments will take place Monday through Thursday only. **In case of emergency**, a special request will need to be authorized by Exelixis Clinical Supplies in order to ship on Friday. If a special drug shipment request is needed, please contact Exelixis Clinical Supplies immediately. The Exelixis Clinical Supplies team can be reached directly at the following email address: Clinical_Supplies@Exelixis.com

5.3 Drug Expiry Date Notification

Exelixis maintains an on-going stability program for all lots of cabozantinib being used in study trials and is responsible for the management of the expiry dates for the cabozantinib supplied. In addition, Exelixis provides notification letters to sites before the expiry date of the affected IP. All expiry date notification letters should be filed in the site study pharmacy binder.

5.4 Drug Receipt and Confirmation

The Study Pharmacist or assigned designee is responsible for proper inspection of each shipment of IP received. At the time of receipt, the Study Pharmacist or assigned designee must provide confirmation that all supplies are intact and in good condition.

Once IP is received and confirmed in good condition, write in the IST Study Identifier on the designated blank line available on the label of the IP bottle(s) (see Attachment 2.0).

If the shipment is damaged, missing, shows signs of tampering, etc., quarantine the shipment in a secure location and contact Exelixis Clinical Supplies immediately. Once

a final decision is made regarding the disposition of any IP placed on quarantine status, you will receive further information regarding the availability or unavailability of the IP.

All IP shipment/receipt documentation must be filed in site study pharmacy binder.

6 INVESTIGATIONAL PRODUCT DISPENSATION/ADMINISTRATION

6.1 Dispensation and Administration

6.1.1 Cabozantinib Dispensation

All cabozantinib should be dispensed in the original container supplied by Exelixis and **should not** be repackaged at any time.

6.1.2 Cabozantinib Administration

For the doses of cabozantinib taken outside the clinic, subjects should fast (with the exception of water) for at least 2 hours after eating an evening meal before taking their dose. After the 2-hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water (minimum of 8 ounces or 240 milliliters) with no more food intake for a minimum of one hour post-dose. If the subject's schedule requires taking cabozantinib during the day, the subject is to be instructed to follow the same fasting recommendations. The subject should take cabozantinib at approximately the same time every day and the subject is to adhere to the fasting requirements described in this section.

6.2 Instructions on Dose Reduction and/or Hold

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

6.3 Subject Dosing Instructions

Refer to Section 6.1.2 of this document for out-patient dosing instructions. Subject compliance with out-patient study treatment regimens will be assessed by the site using standard operating procedures.

7 RECORD KEEPING

All records must be retained and available per site procedures. At the end of the study, the IP records will 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 (i.e., the IND is closed), or until further notification from Exelixis.

8 INVESTIGATIONAL PRODUCT ACCOUNTABILITY PROCEDURES

The study investigator or assigned designee is required to maintain accurate IP accountability records per the site Standard Operating Procedures (SOP).

9 INVESTIGATIONAL PRODUCT DISPOSITION

At no time during the study should IP be returned to Exelixis. Please follow your site's Standard Operating Procedure for destruction of IP. If site is unable to destroy IP on site, the IP will need to be returned to the depot for destruction. Please contact Exelixis Clinical Supplies at Clinical_Supplies@exelixis.com for instructions on returning IP to the depot.

10 PHARMACY MANUAL HISTORY

Pharmacy Manual Version	Effective Date	Change Summary
V3	24-Oct-2017	Revised Version

ATTACHMENT 1.0: SAMPLE OF DRUG REQUEST FORM

EXELIXIS®

SECTION 1: SITE INFORMATION

PROTOCOL:

XL184 – IST_____

STUDY DRUG ORDER FORM

Investigator Name: _____

Contact Person: _____

Site Name &Address: _____

_____

_____

Phone/Fax: _____

Date Requested: _____

Date Required at Site: _____

Requested By: _____

SECTION 2: DRUG REQUEST:

For Clinical Site Use Only:			*For Exelixis Clinical Supplies Use Only:*		
☐ **Initial Supply** ☐ **Resupply**			*Exelixis Order # _____*		
PRODUCT DESCRIPTION (30 Tablets per bottle)	**REQUESTED QUANTITY**	**CURRENT INVENTORY**	**APPROVED QUANTITY**	**LOT NUMBER**	**PART NUMBER**
XL184 20 mg Tab					
XL184 60 mg Tab					
Total # of Active Subjects					
20mg					
40mg					
60mg					

To avoid any delays on shipment order processing, the "Requester" must complete all information requested on the form.

For Exelixis Clinical Supplies Use Only

Shipment Request Approved By:

Print Name / Signature		Date:	

Attachment 2.0: INSTRUCTIONS FOR WRITING IN STUDY IDENTIFIER ON STUDY DRUG BOTTLE

1. Remove the drug bottle(s) from your drug shipment.

2. On the label of the bottle, you will find an empty space under "XL184 (Cabozantinib) 20mg Tablets" or "XL184 (Cabozantinib) 60mg Tablets". (See below for sample label text)

3. Fill in the space by writing in your IST Study Number.
   Note: The IST Study number is on your Exelixis Study Drug Shipment Request Form.

Sample Labels:

XL184 (Cabozantinib) 20mg Tablets

_____

Lot Number: XXXXXXXX DOM: MMM/YYYY

Quantity: 30 Tablets

Take orally as directed by investigator.

Store at Controlled Room Temperature 20°C to 25°C (68°F to 77°F)

Keep out of the reach of children.

Caution: New Drug – Limited by Federal (or United States) law to investigational use.

NSC# 761968

Manufactured By: Patheon, Mississauga, ON L5N 7K0 Canada

For: Exelixis, South San Francisco, CA 94080, Tel: +1 (650) 837-7000

XL184 (Cabozantinib) 60mg Tablets

_____

Lot Number: XXXXXXXX DOM: MMM/YYYY

Quantity: 30 Tablets

Take orally as directed by investigator.

Store at Controlled Room Temperature 20°C to 25°C (68°F to 77°F)

Keep out of the reach of children.

Caution: New Drug – Limited by Federal (or United States) law to investigational use.

NSC# 761968

Manufactured By: Patheon, Mississauga, ON L5N 7K0 Canada

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