A STUDY OF NERATINIB PLUS CAPECITABINE VERSUS LAPATINIB PLUS CAPECITABINE IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER WHO HAVE RECEIVED TWO OR MORE PRIOR HER2-DIRECTED REGIMENS IN THE METASTATIC SETTING (NALA)

NCT01808573

Study Protocol

Amendment 3 13-FEB-2014

A STUDY OF NERATINIB PLUS CAPECITABINE VERSUS LAPATINIB PLUS CAPECITABINE IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER WHO HAVE RECEIVED TWO OR MORE PRIOR HER2-DIRECTED REGIMENS IN THE METASTATIC SETTING (NALA)

Study Protocol Number:	PUMA-NER-1301
Disease Condition:	HER2-Positive Metastatic Breast Cancer
Sponsor's Investigational Product Name/Formulation:	Neratinib Tablets
US IND Number	066783
EudraCT Number	2012-004492-38
Lead Investigator:	[redacted]
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Sponsor's Medical Contact:	[redacted]

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STUDY CONTACTS

Refer to the study reference manual.

PROTOCOL SYNOPSIS

Title: A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2-Directed Regimens in the Metastatic Setting (NALA)

Condition or Disease: Human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC)

Phase of Development	3

Approximate Values			
Number of Patients	600	**Duration of Patient Participation**	28 Months
Number of Centers	200	**Duration of Study**	50 Months

Objectives:

Primary: The co-primary objectives of this study are

- to compare independently adjudicated progression-free survival (PFS) following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive (HER2+) MBC who have received two or more prior HER2-directed regimens in the metastatic setting.
- to compare overall survival (OS) following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in this population.

Secondary: The secondary objectives of this study are to compare between the two treatment groups:

- Investigator-assessed PFS.
- Objective response rate (ORR), duration of response (DOR) and clinical benefit (CBR) (complete response [CR] or partial response [PR] or stable disease [SD] ≥24 weeks).
- Time to intervention for symptomatic metastatic central nervous system (CNS) disease.
- Safety (adverse events [AEs], serious adverse events [SAEs]).
- Health outcomes assessments.

Exploratory:

The exploratory objective of this study is:

- To assess the population pharmacokinetics (PK) of neratinib when administered in combination with capecitabine.

Study Design:

This is a randomized, multi-center, multinational, open-label, active-controlled, parallel design study of the combination of neratinib plus capecitabine versus the combination of lapatinib plus capecitabine in HER2+ MBC patients who have received two or more prior HER2-directed regimens in the metastatic setting. Patients will be randomized in a 1:1 ratio to one of the following treatment arms:

- Arm A: neratinib (240 mg once daily) + capecitabine (1500 mg/m^2 daily, 750 mg/m^2 twice daily [BID])
- Arm B: lapatinib (1250 mg once daily) + capecitabine (2000 mg/m^2 daily, 1000 mg/m^2 BID)

Patients will receive either neratinib plus capecitabine combination or lapatinib plus capecitabine combination until the occurrence of death, disease progression, unacceptable toxicity, or other specified withdrawal criterion.

Patient randomization will be stratified according to:

- The number of previous HER2-directed regimens in the metastatic setting (N = 2 or N ≥3).

- Geographic region (North America vs. Europe, including Israel vs. Rest of World).
- Visceral vs. non-visceral-only disease.
- Estrogen receptor + (ER+) and/or progesterone receptor (PR+) (i.e., hormone receptor +) versus ER- and PR- (i.e., hormone receptor -).

Patients are anticipated to participate in the study for an average of 28 months. This includes approximately 0.5 months for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 18 months for the long-term follow-up phase. Treatment is to be given for as long as tolerated and while there is no disease progression. Patients who permanently discontinue treatment will enter the long-term follow-up phase until death or withdrawal of consent.

Investigational Product, Dose and Administration:

Neratinib + Capecitabine Combination:

- Neratinib dosing: six 40 mg tablets (total daily dose 240 mg) orally, once daily with food, preferably in the morning, continuously in 21-day cycles, with no rest between cycles.
- Capecitabine dosing: 150 mg or 500 mg tablets (total dose of 1500 mg/m^2 daily in 2 approximately evenly divided doses), orally with water within 30 minutes after a meal. Doses are to be taken daily for Days 1 to 14 of a 21-day cycle.

Lapatinib + Capecitabine Combination:

- Lapatinib dosing: five 250 mg tablets (total dose 1250 mg) orally, once daily, 1 hour before or after breakfast, continuously in 21-day cycles, with no rest between cycles.
- Capecitabine dosing: 150 mg or 500 mg tablets (total dose of 2000 mg/m^2 daily, in 2 approximately evenly divided doses), orally with water within 30 minutes after a meal. Doses are to be taken daily for Days 1 to 14 of a 21-day cycle.

Study Population:

Inclusion Criteria

1. Aged ≥18 years at signing of informed consent.
2. Histologically confirmed MBC, current stage IV.
3. Documented HER2 overexpression or gene-amplified tumor (immunohistochemistry [IHC] 3+ or IHC 2+ with confirmatory fluorescence in situ hybridization [FISH]+). (Note: Patients who are IHC 0 or 1+ are not eligible to participate in the study). Tumor samples will be evaluated for HER2 expression by IHC (HercepTest™) and if required for gene amplification by FISH analysis (IQFISH pharmDx™).
4. Prior treatment with at least two (2) HER2-directed regimens for metastatic breast cancer. A new regimen is defined as a modification in a planned course of therapy to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new regimen also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
5. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
6. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
7. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
8. Negative β-human chorionic gonadotropin (hCG) pregnancy test for premenopausal women of reproductive capacity (those who are biologically capable of having children) and for women less than 12 months after menopause.

9. Women of childbearing potential must agree and commit to the use of a highly effective method of contraception, as determined to be acceptable by the Investigator, from the time of informed consent until 28 days after the last dose of the investigational products. Men must agree and commit to use a barrier method of contraception while on treatment and for 3 months after last dose of investigational products.
10. Provide written, informed consent to participate in the study and follow the study procedures.

Exclusion Criteria

1. Received previous therapy with capecitabine, neratinib, lapatinib, or any other HER2-directed tyrosine kinase inhibitor.
2. Received prior therapy resulting in a cumulative epirubicin dose >900 mg/m^2 or cumulative doxorubicin dose >450 mg/m^2. If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 450 mg/m^2 doxorubicin.
3. Any major surgery ≤28 days prior to the initiation of investigational products, or received anti-cancer therapy (including chemotherapy, biological therapy, hormonal therapy, investigational agents, or other anti-cancer therapy) administered ≤21 days prior to the initiation of investigational products.
4. Received radiation therapy ≤14 days prior to initiation of investigational products.
5. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days prior to randomization are eligible to participate in the study).
6. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.
7. QTc interval >0.450 seconds or known history of QTc prolongation or Torsades de Pointes.
8. Screening laboratory assessments outside the following limits:

Laboratory endpoint	**Required limit for exclusion**
Absolute neutrophil count (ANC)	<1500/µL (<1.5 x 10^9/L)
Platelet count	<100,000/µL (<100 x 10^9/L)
Hemoglobin (Hb)	<8 g/dL (transfusions allowed) Transfusions must be at least 14 days prior to randomization.
Total bilirubin	>1.5 x institutional upper limit of normal (ULN)
Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT)	>3 x institutional ULN (>5 x ULN if liver metastases are present)
Creatinine clearance	<50 mL/min (as calculated by Cockroft and Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b]

[a] Cockcroft and Gault, 1976
[b] Levey et al., 1999

9. Active infection or unexplained fever >38.5°C (>101.3°F).
10. Other malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or vulva; c) prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas.
11. Currently breast-feeding.

12. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at screening).
13. Active infection with hepatitis B or hepatitis C virus.
14. Known dihydropyrimidine dehydrogenase deficiency.
15. Known hypersensitivity to 5-fluorouracil or to any component of the investigational products or compounds of similar chemical composition.
16. Unable or unwilling to swallow tablets.
17. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that would, in the Investigator's judgment, make the patient inappropriate for this study.

Efficacy Assessments:

There are 2 co-primary endpoints: independently adjudicated PFS and OS. All patients randomized will be evaluated.

- PFS is defined as disease progression (radiographic or other appropriate modality) or death due to any cause.
  - Efficacy assessment for PFS will be assessed by a blinded, independent, central review of tumor assessments for all patients at screening, and then after every 6 weeks from first dose of investigational product, regardless of treatment schedule modification (e.g., dose delay), until documented disease progression or death due to any cause. Progressive disease (PD) will be independently-assessed using RECIST v1.1.
- Overall survival, defined as the time from randomization to death due to any cause.
  - Survival data will be collected throughout the active treatment phase and during the long-term follow-up phase. Survival follow-up after patient discontinuation of investigational product will be conducted approximately every 12 weeks to assess for survival until patient death or withdrawal of consent.

The secondary endpoints include:

- Comparison of clinically relevant improvements in breast cancer patients with respect to radiographic changes or changes in other appropriate modalities, including (see footnote*):
  - "Investigator-assessed" PFS, assessed by tumor assessments that will occur for all patients at screening, and then after every 6 weeks from first dose of investigational product, regardless of treatment schedule modification (e.g., dose delay), until documented disease progression or death due to any cause;
  - Objective response rate, defined as the proportion of patients demonstrating either a CR or PR during the study;
  - Duration of response is measured from the time at which response criteria were met for CR or PR (whichever status was recorded first) until the first date of recurrence or PD or death;
  - Clinical benefit rate, defined as the proportion of patients who achieved overall tumor response (CR or PR) or SD for at least 24 weeks.
- Time to intervention for symptomatic metastatic CNS disease, defined as date of initiation of intervention or therapy for symptomatic CNS disease determined by the investigator to be due to CNS metastasis. This may include brain, leptomeningeal and epidural metastases including epidural spinal cord compression arising from tumor growth in the epidural space.

* All of the secondary efficacy endpoints including CR, PR, and SD will be assessed by the investigator and by the independent review committee utilizing RECIST v1.1.

Safety Assessments:

Patients receiving at least 1 dose of investigational product will be evaluable for safety. Safety will be assessed based on medical history, vital sign measurements, physical examination findings, electrocardiogram (ECG) results, MUGA or ECHO and laboratory assessments. Adverse events will be graded according to the NCI CTCAE v.4.0. AEs and SAEs will be reported until 28 days after the last dose of investigational product(s) and will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAE occurring any time after the reporting period, it must be promptly reported.

Other Assessments:

Pharmacokinetics:

A population PK study with sparse sampling will be included in the study to assess the variability of neratinib concentration when administered in combination with capecitabine among individuals in the target patient population. At selected study centers, PK samples will be collected from approximately 100 patients in the neratinib plus capecitabine arm (Arm A) at Cycle 1, on Days 1 and 15.

Health Outcomes Assessment:

The following health outcomes assessments will be completed by patients:

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), version 3
- EORTC QLQ-BR23 (breast cancer-specific questionnaire)
- The EuroQol (EQ-5D-5L) multi-dimensional health status questionnaire

Health outcomes assessments will be performed at screening, every 6 weeks during the active treatment period and at treatment discontinuation.

Criteria for Patient Withdrawal:

A patient must be discontinued from investigational product(s) (IP) in the following circumstances:

- if more than 2 dose reductions are required (Appendix 2)
- if IP is withheld >28 days due to AE
- disease progression
- initiation of alternative anti-cancer therapy, including chemotherapy, radiotherapy, and cancer-related surgery
- pregnancy
- investigator or patient request

A patient may withdraw from the entire study, including follow-up, at any time at the discretion of the investigator, at the patient's request, if the patient is lost to follow-up, or if the study is terminated prematurely.

Statistical Methods:

The co-primary endpoints are OS and independently adjudicated PFS, which will be determined by disease progression (disease progression demonstrated by radiographic imaging or other appropriate modality) or death due to any cause. Tumor evaluations for PD will be performed by a central review vendor.

Secondary efficacy endpoints include Investigator-assessed PFS, ORR, DOR, and CBR (CR, PR or SD ≥24 weeks). Other secondary endpoints include time to intervention for symptomatic CNS disease, AEs and SAEs, and health outcomes assessments.

Sample Size:

The co-primary endpoints will be analyzed using an overall Type I error rate of 0.01 for PFS and 0.04 for OS. To detect a hazard ratio (control versus treatment) of 0.70 with approximately 85% power, 419 PFS events (PD/deaths) are required to be observed; this assumes a median (intent-to-treat [ITT]) PFS of 8.0 months (34.7

weeks) for the experimental arm (neratinib plus capecitabine) and 5.6 months (24.3 weeks) for the control arm (lapatinib plus capecitabine). It is expected that the 419th event will be observed at approximately 26 months after the first subject is enrolled. At this time, an interim analysis on OS will also be performed. For the OS endpoint, a group sequential method will be employed to maintain the overall Type I error rate at 0.04. Specifically, O'Brien-Fleming boundaries will be calculated to create appropriate critical values to which the log rank statistic will be compared. To detect a hazard ratio (control versus treatment) of 0.725 with approximately 85% power, 378 events (deaths) are required to be observed; this assumes a median ITT OS of 30.3 months for the experimental arm (neratinib plus capecitabine) and 22.0 months for the control arm (lapatinib plus capecitabine). Approximately 600 patients will be enrolled and randomized equally between the two treatment arms.

Patients will be stratified according to whether they are hormone receptor positive or negative, the number of previous HER2-directed regimens in the metastatic setting (N = 2 or N ≥3), their geographic region (North America vs. Europe, including Israel vs. Rest of World), and disease category (visceral vs. non-visceral only).

Statistical Analysis:

The primary efficacy analysis will be performed on the ITT population defined as all patients randomized into the study. Patients receiving at least one dose of investigational product will be evaluable for safety.

Efficacy

When 419 PFS events have occurred the primary PFS analysis will be performed. The median time to PFS and corresponding two-sided 95% confidence intervals will be calculated using the product limit estimator and displayed using a Kaplan-Meier graph, by treatment group. A log-rank test stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, visceral disease, and geographic region will be used to test the null hypothesis of no difference in the time to PFS between the two treatment groups at the alpha level of 0.01. When 378 deaths have occurred, the primary OS analysis (final analysis) will be performed, using similar methods. A log-rank test controlling for hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, visceral disease, and geographic region strata will be used to test the null hypothesis of no difference in the hazard between the two treatment groups at the alpha level of 0.038.

The treatment difference in the secondary efficacy endpoints of ORR and CBR will be analyzed using a Cochran-Mantel-Haenzel (CMH) Chi-square test, stratified by the hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, geographic region, and disease category (visceral vs. non-visceral only). The treatment difference in the secondary efficacy endpoints of DOR, and Investigator-assessed PFS will be analyzed using a product limit estimate of the median time to event. Differences between treatment groups will be examined using a log rank test statistic stratified by hormone receptor status, prior HER2-directed regimens in the metastatic setting, geographic region, and disease category (visceral vs. non visceral only) similar to the analysis for the primary endpoint. All time-to-event endpoints, including time to intervention for symptomatic CNS disease, will be displayed using Kaplan-Meier survival plots. Health outcomes assessments (EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-5L) will be analyzed using a random effects mixed model with treatment, time, number of prior HER2-directed regimens in the metastatic setting (binary), geographic region, site of metastases, and the treatment by time interaction.

Subjects who discontinue therapy early will be censored at their last available time point. Sensitivity analyses will be performed to investigate the impact of differential dropout between the 2 treatment groups on the treatment effect estimate.

Safety

All safety endpoints will be summarized by treatment group and visit when appropriate. Adverse events and

serious adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system v.15 or later, and they will be tabulated by organ system and preferred term. All AEs will be graded according to the NCI CTCAE v.4.0. Differences in the incidence of the most common AEs and SAEs between the two treatment groups will be investigated using a CMH chi-square test, stratified on hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, geographic region, and disease category (visceral vs. non-visceral only).

Interim Analysis:

No interim PFS or OS analysis for early stopping is planned. An interim analysis of OS will be conducted at the time of the final PFS analysis (at the alpha level of 0.002 at the interim analysis and 0.038 for the final analysis).

Final Analysis:

A final PFS analysis will be conducted when 419 PFS events have occurred.

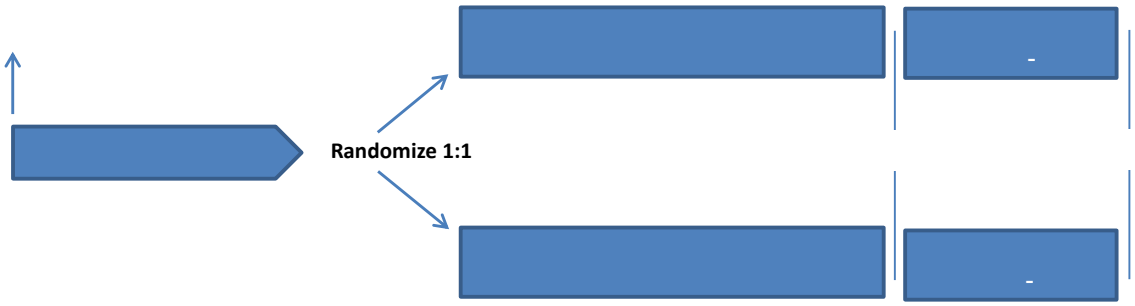
A final OS analysis will be conducted when 378 deaths have occurred.

An analysis of all efficacy and safety endpoints will occur after the long-term follow-up phase has been completed.

Study Design Diagram / Schedule of Procedures:

A diagram of the study design is provided below in Figure 1. A schedule of procedures is included in Appendix 1.

Figure 1. Study Schema of PUMA-NER-1301



PFS: progression-free survival; OS: overall survival.

End of treatment is defined as documented disease progression, unacceptable toxicity or withdrawal of consent.

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5-FU	5-fluorouracil
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenzel
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DM1	Emtansine
DOR	duration of response
EC	Ethics Committee
ECD	extracellular domain
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor (also known as HER1)
EIU	Exposure-In-Utero
ECG	electrocardiogram, electrocardiography
ErbB	epidermal growth factor family of trans-membrane receptors (also known as HER)
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life
EOS	end of study
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
hCG	human chorionic gonadotropin
GCP	Good Clinical Practice
Hct	hematocrit
HER	human epidermal growth factor receptor
HER2+	human epidermal growth factor receptor 2 positive

Hb	hemoglobin
HIPAA	Health Insurance Protection and Portability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IM	intramuscular
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous(ly)
LD	longest diameter
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic
PPE	palmar-plantar erythrodysesthesia syndrome
PR	partial response, progesterone receptor
QLQ	Quality of Life Questionnaire
RBC	red blood cell
RDW	red blood cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
RoW	rest of world
SAD	short axis diameter
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	stable disease
SLD	sum longest diameter

SPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TD	treatment discontinuation
T-DM1	trastuzumab emtansine
TdP	Torsade de Pointes
TEAE	treatment-emergent adverse event
TID	three times daily
TTP	time to tumor progression
ULN	upper limit of normal
US	United States (of America)
WBC	white blood cell
WHODrug	World Health Organization Drug Reference List

2 INTRODUCTION

2.1 Background

2.1.1 General Therapeutic Area

Approximately 15-20% (Ahn et al., 2012; Saini et al, 2011) of women with breast cancer have human epidermal growth factor receptor 2 positive (HER2+) cancer, which is associated with aggressive disease and poor prognosis (Slamon et al, 1987). The human epidermal growth factor receptor 2 (HER2)/neu gene is a member of the family of EGFR/ErbB genes: amplification or overexpression is associated with an aggressive disease biology, including enhanced cell proliferation and reduced progression-free survival (PFS), and overall survival (OS) (Slamon et al, 1987; Zhang et al, 2007; Badache and Goncalves 2006; Slamon et al., 1989). Compared with female breast cancer, male breast cancer cases are more often hormonal receptor (estrogen receptor/progesterone receptor) positive and HER2 negative, but treatment of male breast cancer patients follows the same indications as female postmenopausal breast cancer with surgery, systemic therapy and radiotherapy (Ottini et al., 2010).

2.2 Current Therapies

2.2.1 The Epidermal Growth Factor Receptor Family (ErbB Receptors)

Members of the epidermal growth factor family of trans-membrane receptors (ErbB family) are potent mediators of normal cell growth and development and are expressed in various tissues of epithelial, mesenchymal and neuronal origin (Baselga and Swain, 2009). The ErbB family consists of four closely related type 1 trans-membrane tyrosine kinase receptors: epidermal growth factor receptor (EGFR; also known as ErbB1 and HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4).

Aberrant expression of HER1, HER2 and HER3 are linked to development of many epithelial cancers including colorectal, gastric, breast and head and neck cancers. These membrane-spanning proteins receive extracellular signals from small peptide ligand molecules, including epidermal growth factor-like molecules, transforming growth factor-α and neuregulins. Under normal physiological conditions, activation of the HER receptors is controlled by the spatial and temporal expression of their ligands (Yarden and Sliwkowski, 2001). Ligand binding triggers intracellular signaling through a complex and tightly controlled array of signaling pathways that together drive and regulate many cellular functions, including cell proliferation and organ development and repair. Binding of ligands to extracellular parts of HER1, HER3 and HER4 will result in dimerization and initiates a series of signaling cascades that includes

mitogen-activated protein kinase, phosphoinositide-3kinase (PI3K), Akt, and mammalian target of rapamycin (Garrett and Arteaga, 2011).

Each receptor comprises an extracellular domain (ECD) at which ligand binding occurs: an alpha-helical trans-membrane segment and an intracellular protein tyrosine kinase domain (Olayioye et al., 2000). Receptor dimerization is an essential requirement for signaling activity of these receptors and can occur between two different HER receptors (hetero-dimerization) or between two molecules of the same receptor (homo-dimerization) (Olayioye et al., 2000; Ferguson et al., 2003). HER homodimers weakly perpetuate signals compared with heterodimers (Yarden and Sliwkowski, 2001). As the natural ligand for HER2 has not been identified, the receptor is presumed to exert its effects via formation of heterodimers with other HER family members, and is thought to be the preferred dimerization partner for the other receptors (Rosen et al., 2010). In fact, heterodimer formation with HER2 has been shown to increase the affinity of ligand binding to the dimerization partner (Graus-Porta et al., 1997). Dimerization of HER3, which lacks intrinsic kinase activity, with HER2 induces phosphorylation of HER3, which then activates the PI3K and Akt pathways (Graus-Porta et al., 1997).

2.2.2 Cancer Therapies Targeting HER Receptors

2.2.2.1 *Trastuzumab*

Trastuzumab, the first agent approved for treatment of HER2+ breast cancer, is a monoclonal antibody that binds to the juxtamembrane portion of the HER2/neu receptor, resulting in inhibition of tumor proliferation (Goldenberg 1999). Possible mechanisms by which trastuzumab might decrease signaling include prevention of HER2-receptor dimerization, increased endocytotic destruction of the receptor, inhibition of shedding the extra-cellular domain, and immune activation (Valabrega et al., 2007). Preclinical models suggest that trastuzumab recruits immune effector cells that are responsible for antibody-dependent cytotoxicity (Weiner and Adams, 2000). Trastuzumab was first approved for use in the treatment of HER2-amplified breast cancer in the US in 1998.

2.2.2.2 *Pertuzumab [Perjeta™]*

Pertuzumab (Perjeta) is a monoclonal antibody that binds HER2 at a different epitope of the HER2 extracellular domain (subdomain II) than that at which trastuzumab binds (Baselga et al., 2012) and prevents HER2 from dimerizing with other ligand-activated HER receptors, most notably HER3 (Baselga and Swain, 2009; Agus et al., 2002). The HER2-HER3 heterodimer is considered to be the most potent signaling pair (Agus et al., 2002), driving cell proliferation in HER2+ cancer (Lee-Hoeflich et al., 2008; Hsieh and Moasser, 2007). In recent studies, the addition of pertuzumab to combination therapy has led to improvements in PFS in patients with

HER2+ metastatic breast cancer (MBC) and higher response rates in the preoperative setting (Murphy and Morris, 2012).

2.2.2.3 *Pertuzumab in Combination with Trastuzumab*

Although treatment with trastuzumab in addition to chemotherapy (as compared with chemotherapy alone) significantly improves PFS and OS among patients with HER2+ MBC, in most patients, the disease progresses (Nahta and Esteva 2007). Because pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action, the combination of these two agents, provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity than either agent alone in HER2+ tumor models (Lee-Hoeflich et al., 2008; Scheuer et al., 2009). In Phase 2 studies, a pertuzumab-trastuzumab regimen showed activity in patients with HER2+ MBC (Baselga et al. 2010; Portera et al., 2008) and in patients with early breast cancer (Gianni et al., 2010).

The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study assessed the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel (control group), as first-line treatment for patients with HER2+ MBC who had not received chemotherapy or biologic therapy for their metastatic disease (Baselga et al., 2012). Based on an interim analysis (on 43% of the total number of events planned for the final analysis), treatment with pertuzumab plus trastuzumab plus docetaxel compared with the control group resulted in a significant reduction in the risk of progression or death and an increase of 6.1 months in median PFS (Baselga et al., 2012). The median PFS in the control group (12.4 months) was similar to that among HER2+ MBC patients in two other randomized studies, who were treated with the combination of trastuzumab and docetaxel (11.7 months (Marty et al., 2005) and 11.1 months (Valero et al., 2011). CLEOPATRA findings suggest that targeting HER2+ tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action results in a more comprehensive blockade of HER2 and highlights the clinical importance of preventing the ligand-dependent formation of HER2 dimers in order to silence HER2 signaling to the greatest extent possible (Baselga and Swain, 2009; Yarden and Sliwkowski, 2001).

Pertuzumab received approval in the US in 2012 for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

2.2.2.4 *Ado-trastuzumab Emtansine (T-DM1[Kadcyla™])*

Ado-trastuzumab emtansine (T-DM1 [Kadcyla]) is an antibody-drug conjugate that combines HER2-targeted delivery of the potent antimicrotubule agent emtansine (DM1), a derivative of the antimicrotubule agent maytansine, with the antitumor activity of trastuzumab (Lewis Phillips et

al., 2008; Remillard et al., 1975; Cassady et al., 2004; Widdison et al., 2006; Junttila et al., 2011). In T-DM1, trastuzumab and DM1 are covalently linked via a stable thioether linker (*N*-maleimidomethyl) cyclohexane-1-carboxylate, which is thought to limit the exposure of normal tissue to DM1 (Krop et al., 2010; Burris et al., 2011). Antitumor activity was established in a proof-of-concept Phase 2 study of single-agent T-DM1 in patients with HER2+ MBC, who had progressed while receiving HER2-directed therapy (Burris et al., 2011). Furthermore, in a single-arm Phase 2 study, T-DM1 demonstrated efficacy in patients with HER2+ MBC who previously received all standard HER2-directed therapies (trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine) (Krop et al., 2012).

Primary results from the EMILIA study (a Phase 3, randomized, multicenter study of T-DM1 compared with lapatinib plus capecitabine in patients with HER2+ locally advanced or MBC, previously treated with a trastuzumab-based regimen and a taxane) showed a significant and clinically meaningful improvement with T-DM1 in PFS compared with lapatinib plus capecitabine (Blackwell et al., 2012). Other end points supported T-DM1 as an active and well-tolerated novel therapy for HER2+ advanced breast cancer. T-DM1 is approved in the US for patients with HER2-positive MBC who have previously received trastuzumab and a taxane separately or in combination.

2.2.2.5 *Lapatinib*

Another HER2-targeted agent is lapatinib, an oral, selective, reversible, small molecule tyrosine kinase inhibitor that targets the tyrosine kinase domains of both HER1 and HER2 (Rusnak et al., 2011; Gomez et al., 2008). In vitro studies confirmed that lapatinib inhibits growth (Rusnak et al., 2011; Xia et al., 2002) and can lead to cell arrest or apoptosis (Rusnak et al., 2001; Xia et al., 2002; Konecny et al., 2006) in human tumor cells overexpressing HER1 or HER2. Furthermore, lapatinib treatment has been shown to inhibit the growth of HER2-overexpressing human breast cancer cells that do not respond to trastuzumab after long-term conditioning (Konecny et al., 2006). Investigations of lapatinib monotherapy conducted in highly refractory MBC patients showed modest cytoreduction and disease stabilization in a trastuzumab-refractory setting (Blackwell et al., 2005).

2.2.2.6 *Lapatinib in Combination with Capecitabine*

Lapatinib was first approved in the US in 2007 for use in combination with capecitabine for the treatment of patients with advanced or MBC whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

The efficacy of lapatinib in combination with capecitabine is summarized in Table 1. Information from both the US Package Insert (independently-assessed) and European Summary

of Product Characteristics (SPC) (Investigator-assessed) are included to provide a broader regional perspective.

Table 1. Efficacy of Lapatinib + Capecitabine

Products	ORR (%)	Median TTP (weeks)	Median OS (weeks)
Lapatinib + Capecitabine	23.7[a]	27.1[a] 23.9[b]	75.0[a] 74.0[b]

Abbreviations: ORR: objective response rate, OS: overall survival; TPP: time to tumor progression.
[a] Tykerb® (lapatinib) tablets [US package insert]
[b] Tyverb® 250 mg film-coated tablets (SPC)

2.2.3 Neratinib

2.2.3.1 *Preclinical Data*

Neratinib is an orally available small molecule that inhibits HER1, HER2 and HER4 at the intracellular tyrosine kinase domains, a mechanism of action that is different from trastuzumab as well as lapatinib. Neratinib reduces HER1 and HER2 autophosphorylation, downstream signaling, and the growth of HER1 and HER2 dependent cell lines. Neratinib most likely inhibits kinase activity through irreversible binding at a targeted cysteine residue in the adenosine triphosphate binding pocket of the receptor. Preclinical data suggest that neratinib will have antitumor activity in HER1 and/or HER2-expressing carcinoma cell lines, with cellular IC_{50} <100 nM (Rabindran et al., 2004).

Neratinib may have advantages over other HER2 inhibitors, due to its ability to inhibit both HER1 and HER2, and to inhibit irreversibly. Breast cancer cells may become resistant to trastuzumab on the basis of ECD truncated HER2 receptor, which can no longer be recognized by the antibody (Xia et al., 2004), or because of co-activation of HER1 signaling (Rampaul et al., 2005; Zaczek et al., 2005). However, since neratinib acts on the intracellular tyrosine kinase domain, such cells are likely to maintain sensitivity to neratinib (Mosesson and Yarden, 2004).

In vivo, neratinib is active in HER2 and HER1-dependent tumor xenograft models, when administered orally on a once daily schedule. Overall, neratinib is less potent against HER1-dependent tumors than HER2-dependent tumors *in vivo*, although it has equivalent activity against the two kinases *in vitro*.

Further pre-clinical information on neratinib is provided in the current Investigator's Brochure.

2.2.3.2 *Neratinib Phase 1 and Pharmacokinetic Data*

Further information on the Phase 1 and PK data for neratinib is provided in the current Investigator's Brochure.

2.2.3.3 *Neratinib Single-Agent Activity in Patients with HER2+ Breast Cancer*

Both the ability of neratinib to concurrently block signal transduction through the three active tyrosine kinase HER receptors and its irreversible binding and prolonged inhibition of these growth-promoting pathways provide the opportunity to further improve the clinical benefit of this therapeutic approach in HER2+ MBC patients. Early clinical data have demonstrated the activity of neratinib in patients who have already failed other small molecule or antibody-based anti-HER receptor therapies, suggesting the ability of this agent to overcome drug resistance in this refractory patient population.

In the single-agent, first in human, Phase 1 study (3144A1-102-US) of neratinib in solid tumor, a 32% objective response rate (ORR) was observed among patients with trastuzumab refractory HER2 overexpressing disease (Wong et al., 2009). Specifically, 8 of 25 patients had partial response (PR). Among the responders, 2 PRs occurred at neratinib doses of 120 or 180 mg per day, which was below the recommended monotherapy dose. All of these responders had prior trastuzumab therapy, notably 6 patients had received at least four trastuzumab-based therapies. Additionally, all had received prior anthracycline and gemcitabine, and the majority (7/8) had received prior taxane therapy. Six patients had also received prior capecitabine therapy and 3 had received prior 5% fluorouracil treatment. This activity in trastuzumab-resistant breast cancers in the Phase 1 setting compares favorably to the response rates reported in two Phase 2 studies of the *reversible* dual kinase inhibitor, lapatinib, in a similar patient population (Blackwell et al, 2005).

An open-label, multicenter, Phase 2 study evaluated the efficacy and safety of neratinib 240 mg daily, in patients with and without prior trastuzumab treatment, who had advanced HER2+ breast cancer. The primary end point, the 16-week PFS rates, was 59% and 78% in prior trastuzumab-treated patients and trastuzumab-naïve cohorts, respectively (Burstein et al., 2010). The ORR was 24% and 56%, respectively, and the median PFS times were 22.3 and 39.6 weeks, respectively. Mean steady-state trough concentrations for the 240 mg daily dose exceeded concentrations needed to inhibit autophosphorylation of HER2 in preclinical models (Rabindran et al., 2004).

The most common adverse events (AE) were diarrhea, nausea, vomiting, and fatigue. Diarrhea was the most frequent Grade 3 to 4 AE, occurring in 30% of patients with prior trastuzumab treatment and in 13% of trastuzumab-naïve patients, which resulted in dose reductions of 29% and 4% of patients, respectively. However, treatment discontinuation (TD) occurred in only one patient due to diarrhea (Grade 2). No neratinib-related Grade 3 or 4 cardiotoxicity was reported.

Additional information regarding previous clinical studies of neratinib for treatment of HER2+ breast cancer is provided in the current Investigator's Brochure.

2.2.3.4 *Neratinib in Combination with Capecitabine*

In a Phase 1/2 clinical study (3144A1-2206-WW) investigating the combination of neratinib plus capecitabine, the maximum tolerated dose (MTD) of neratinib 240 mg was established in combination with capecitabine 1500 mg/m^2 in patients with solid tumors. Subsequent investigation of this dose regimen in patients with HER2+ advanced breast cancer demonstrated that this combination treatment was clinically active and has a manageable toxicity profile.

In the study, clinical responses at the MTD were observed in 63% of patients (64% of those with no prior lapatinib exposure and 57% of those with prior lapatinib), while median durations of response were 46 and 48 weeks, respectively. This is a slightly higher response rate and similar duration of response (DOR) to that observed in previous neratinib monotherapy studies, but in a full study population previously treated with trastuzumab (Burstein et al., 2010; Wong et al., 2009); an ORR of 29% with neratinib monotherapy has also been reported (Martin et al., 2011). In this study, all patients progressed to previous trastuzumab-based therapy, and median PFS with neratinib plus capecitabine was 40 weeks in the lapatinib-naive cohort and 36 weeks in the lapatinib-treated cohort. These results compare favorably with those previously observed in the monotherapy study for patients who received prior trastuzumab (22 weeks) (Geyer et al., 2006). The results of this study suggest that the combination of neratinib plus capecitabine may have superior efficacy in patients with prior therapy with anti HER2-targeted therapies.

The results of this Phase 1/2 study also compare favorably with results obtained from the combination of lapatinib plus capecitabine in an indirect comparison. In a Phase 3 study, ORR (44.2%), clinical benefit rate (CBR) (57.7%), and PFS (6.34 months) with lapatinib plus capecitabine were lower than was observed with neratinib plus capecitabine in the Phase 1/2 study (Xu et al., 2011).

The combination of neratinib plus capecitabine was associated with an acceptable safety and tolerability profile in the Phase 1/2 study. Diarrhea was the most common Grade 3/4 AE in the study (reported by 23% of patients), although only 4 patients discontinued treatment due to the event (6%), which is similar to previous experience in neratinib monotherapy studies (Burstein et al., 2010; Wong et al., 2009). Diarrhea typically occurred within a few days of neratinib initiation (median, 2 days) and was most often managed by a dose delay or reduction. Across previous neratinib studies, diarrhea typically occurred within 2-8.5 days of neratinib initiation and was generally managed with dose adjustments or antidiarrheal medications (Burstein et al., 2010; Wong et al., 2009).

The most frequent toxicities reported with capecitabine monotherapy are palmar-plantar erythrodysesthesia syndrome (PPE) and gastrointestinal events. While the incidence of PPE (all grades, 47%) in this study was similar to the range reported in capecitabine monotherapy studies (37% to 60%), the incidence of diarrhea was higher (all grades, 88% compared with 5% to 58%

reported in monotherapy studies) (Burstein et al., 2010; Wong et al., 2009), as may be expected from the combination of two drugs that are associated with gastrointestinal effects. Overall, no unexpected toxicity was observed in patients receiving neratinib plus capecitabine, and few patients discontinued treatment due to toxicity.

Further details can be found in the current Investigator's Brochure which contains comprehensive information on the investigational product.

2.3 Study Rationale

The use of taxanes, anthracyclines, and trastuzumab early in the treatment of HER2+ MBC has become standard practice. In patients whose HER2 disease recurs after adjuvant/neoadjuvant trastuzumab therapy and in patients who initially present with advanced metastatic HER2 disease, treatment with trastuzumab in combination with a chemotherapy regimen is usually prescribed. Almost all patients receiving trastuzumab alone or in combination with other drugs for HER2 overexpressing MBC ultimately progress. The clinical benefit of continuing trastuzumab after progression in the first-line metastatic setting has not been definitively established in prospective clinical studies. It is hypothesized that sensitivity to trastuzumab may be retained and that the combination of trastuzumab plus another chemotherapy agent may be preferable to chemotherapy alone in the second-line setting (Pusztai and Esteva 2006; vonMinckwitz et al., 2009). This may explain the widespread acceptance and use of trastuzumab plus a different cytotoxic agent in the second-line setting (Love, 2004).

After multiple treatment regimens with trastuzumab and possibly lapatinib, it is hypothesized that the tumor may no longer be sensitive to the existing HER2 agents. Consequently, the continuing development of new anti-HER2 strategies is needed, particularly for patients whose disease has progressed on prior regimens.

The current multicenter, multinational, randomized, controlled clinical study is designed to compare OS and independently-assessed PFS following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ MBC who have received two or more prior HER2-directed regimens in the metastatic setting.

Further information on the benefits and risks of neratinib in this patient population is provided in the current Investigator's Brochure.

3 STUDY OBJECTIVES

3.1 Primary Objective

The co-primary objectives of this study are:

- to compare independently adjudicated PFS following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ MBC who have received two or more prior HER2-directed regimens in the metastatic setting.
- to compare OS following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in this population.

3.2 Secondary Objectives

The secondary objectives of this study are to compare between the two treatment groups:

- Investigator-assessed PFS.
- Objective response rate (ORR), duration of response (DOR) and clinical benefit rate (CBR) (complete response [CR] or partial response [PR] or stable disease [SD] ≥24 weeks).
- Time to intervention for symptomatic metastatic central nervous system (CNS) disease.
- Safety (AEs, serious adverse events [SAEs]).
- Health outcomes assessments.

3.3 Exploratory Objective

The exploratory objective of this study is:

- To assess the population PK of neratinib when administered in combination with capecitabine.

4 OVERALL DESIGN AND PLAN OF THE STUDY

4.1 Study Design

This is a randomized, multi-center, multinational, open-label, active-controlled, parallel design study of the combination of neratinib plus capecitabine versus the combination of lapatinib plus capecitabine in HER2+ MBC patients, who have received two or more prior HER2-directed regimens in the metastatic setting.

Patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A: neratinib (240 mg once daily) + capecitabine (1500 mg/m^2 orally daily, 750 mg/m^2 twice daily [BID])
- Arm B: lapatinib (1250 mg once daily) + capecitabine (2000 mg/m^2 orally daily, 1000 mg/m^2 BID)

Following a 21-day screening period (Section 9.1), eligible patients will be randomized to Arm A or Arm B. Baseline assessments will be performed prior to randomization. Following randomization, patients will participate in the active treatment phase, consisting of 21-day treatment cycles (Section 9.2). Investigational products will be administered orally by patients as described in Section 6.1. Neratinib and lapatinib are to be taken continuously, in 21-day cycles, with no rest between cycles. Capecitabine will be taken on Days 1 to 14 of each 21-day cycle.

Clinic visits during the active treatment phase are planned on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent cycle. Assessments required throughout the study are summarized in the Schedule of Procedures (Appendix 1) and a diagram of the study schema is provided in Figure 1.

Patients may be discontinued from investigational product(s) or from the study, as described in Sections 10.1, 10.2 and 11.

The co-primary endpoints are independently adjudicated PFS and OS. The secondary endpoints are investigator-assessed PFS, ORR, DOR, CBR (CR, PR or SD ≥24 weeks), health outcomes assessments, time to intervention for symptomatic metastatic CNS disease, AEs and SAEs (graded according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0]). An interim analysis of OS will be performed at the time of final PFS analysis (Section 12.6).

Approximately 600 patients will be enrolled at approximately 200 centers in North America, Europe including Israel, and the Rest of World (RoW). See Section 12.7 for a discussion of sample size.

Patients are anticipated to participate in the study for an average of 28 months. This includes approximately 0.5 months for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 18 months for the long-term follow-up phase. Patients who permanently discontinue treatment will enter the long-term follow-up phase (Section 9.5 until death or withdrawal of consent (Section 10.2).

The approximate duration of the study is 50 months, which is the time estimated to reach the required 378 OS events. The end of study (EOS) will occur as of the date of the last visit of the last patient undergoing the study. In the event that the EOS is declared earlier (e.g., OS primary endpoint is met), patients who continue to receive clinical benefit from neratinib plus capecitabine will be offered the opportunity to continue to receive this combination via a treatment extension study or expanded access protocol. Patients who continue to derive clinical benefit from lapatinib plus capecitabine will be provided the opportunity to receive these marketed therapies as well.

4.2 Randomization and Blinding

4.2.1 Randomization Scheme

Randomization will be managed and maintained centrally through an automated Interactive Voice Response System/Interactive Web Response System. Patients will be randomized in a 1:1 ratio to one of the two treatment arms.

Randomization will be stratified according to:

- The number of previous HER2-directed regimens in the metastatic setting (N = 2 or N ≥3).
- Geographic region (North America vs. Europe, including Israel vs. RoW)
- Visceral vs. non-visceral only disease
- Estrogen receptor+ (ER+) and/or progesterone receptor (PR+) (i.e., hormone receptor +) versus ER- and PR- (i.e., hormone receptor -).

4.2.2 Enrollment and Randomization of Patients to Treatment

Once eligibility is confirmed, patients will be randomized to a treatment group according to the randomization schedule. All patients must commence treatment with investigational products no later than 14 days after randomization. Patients who do not meet the eligibility criteria will not be randomized in the study, but may be rescreened up to two times at the Investigator's discretion.

4.2.3 Blinding and Breaking the Blind

This is an open-label study.

5 STUDY POPULATION

5.1 Inclusion Criteria

Each patient will be entered into this study only if she/he meets all of the following criteria:

1. Aged ≥18 years at signing of informed consent.
2. Histologically confirmed MBC, current stage IV.
3. Documented HER2 overexpression or gene-amplified tumor (immunohistochemistry [IHC] 3+; or IHC 2+ with confirmatory fluorescence in situ hybridization [FISH]+). (Note: Patients who are IHC 0 or 1+ are not eligible to participate in the study). Tumor samples will be evaluated for HER2 expression by IHC (HercepTest™) and if required for gene amplification by FISH analysis (IQFISH pharmDx™).
4. Prior treatment with at least two HER2-directed regimens for metastatic breast cancer. A new regimen is defined as a modification in a planned course of therapy to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity (Rajkumar et al., 2011). A new regimen also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
5. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1 (Eisenhauer et al., 2009), see Appendix 7). Specifically, no ascites, pleural or pericardial effusions, osteoblastic bone metastases, or carcinomatous lymphangitis of the lung as the only lesion are allowed.
6. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
7. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1 (see Appendix 3).
8. Negative β-human chorionic gonadotropin (hCG) pregnancy test for premenopausal women of reproductive capacity (those who are biologically capable of having children) and for women less than 12 months after menopause.
9. Women of childbearing potential must agree and commit to the use of a highly effective method of contraception, as determined to be acceptable by the Investigator, from the time of informed consent until 28 days after the last dose of the investigational products. Men must agree and commit to use a barrier method of contraception while on treatment and for 3 months after last dose of investigational products.

10. Provide written, informed consent to participate in the study and follow the study procedures.

5.2 Exclusion Criteria

A patient will be excluded from this study if she/he meets any of the following criteria:

1. Received previous therapy with capecitabine, neratinib, lapatinib, or any other HER2-directed tyrosine kinase inhibitor.
2. Received prior therapy resulting in a cumulative epirubicin dose >900 mg/m^2 or cumulative doxorubicin dose >450 mg/m^2. If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 450 mg/m^2 doxorubicin.
3. Any major surgery ≤28 days prior to the initiation of investigational products, or received anti-cancer therapy (including chemotherapy, biological therapy, hormonal therapy, investigational agents, or other anti-cancer therapy) administered ≤21 days prior to the initiation of investigational products.
4. Received radiation therapy ≤14 days prior to initiation of investigational products.
5. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days prior to randomization are eligible to participate in the study).
6. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.
7. QTc interval >0.450 seconds or known history of QTc prolongation or Torsades de Pointes.
8. Screening laboratory assessments outside the following limits:

Laboratory endpoint	**Required limit for exclusion**
Absolute neutrophil count (ANC)	<1500/µL (<1.5 x 10^9/L)
Platelet count	<100,000/µL (<100 x 10^9/L)
Hemoglobin (Hb)	<8 g/dL (transfusions allowed) Transfusions must be at least 14 days prior to randomization.
Total bilirubin	>1.5 x institutional upper limit of normal (ULN)
Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT)	>3 x institutional ULN (>5 x ULN if liver metastases are present)
Creatinine clearance	<50 mL/min (as calculated by Cockroft and Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])

[a] Cockcroft and Gault, 1976
[b] Levey et al., 1999

9. Active infection or unexplained fever >38.5°C (101.3°F).
10. Other malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or vulva; c) prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas.
11. Currently breast-feeding.
12. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 (NCI CTCAE v.4.0) diarrhea of any etiology at screening).
13. Active infection with hepatitis B or hepatitis C virus.
14. Known dihydropyrimidine dehydrogenase deficiency.
15. Known hypersensitivity to 5-fluorouracil or to any component of the investigational products or compounds of similar chemical composition.
16. Unable or unwilling to swallow tablets.
17. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that would, in the Investigator's judgment, make the patient inappropriate for this study.

6 INVESTIGATIONAL PRODUCTS AND ADMINISTRATION

6.1 Investigational Product Administration

6.1.1 Neratinib Plus Capecitabine

Neratinib

Neratinib investigational product will be supplied as 40 mg film-coated tablets packaged in bottles with desiccant.

Neratinib (240 mg initial dose; provided as six 40 mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. Neratinib should be taken with food, in the morning.

Neratinib is to be taken continuously in 21-day cycles, with no rest between cycles.

Capecitabine

Capecitabine investigational product is available as 150 mg and 500 mg film-coated tablets.

Capecitabine (total dose of 1500 mg/m^2 daily, in 2 approximately evenly divided doses) will be self-administered orally by patients, starting with Cycle 1/Day 1. Doses are to be taken daily on Days 1 to 14 of each 21-day cycle. Capecitabine should be taken with water within 30 minutes after a meal.

During treatment with neratinib plus capecitabine, patients should be monitored for conditions that may require dose to be held or discontinued, as described in Appendix 2. Careful attention should be paid to the onset of diarrhea or hand-foot syndrome in particular, and early dose adjustment or prophylactic therapy should be implemented as described in Appendix 2.

Daily dosing of neratinib plus capecitabine should continue until a criterion for treatment withdrawal or study withdrawal is met (see Sections 10.1 and 10.2, respectively).

6.1.2 Lapatinib Plus Capecitabine

Lapatinib

Lapatinib investigational product is available as 250 mg film-coated tablets.

Lapatinib (1250 mg initial dose; provided as five 250 mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. The total daily dose of lapatinib should be taken 1 hour before or after breakfast; daily doses should not be divided.

Lapatinib is to be taken continuously in 21-day cycles, with no rest between cycles.

Refer to the lapatinib (Tykerb®) US Package Insert and/or the (Tyverb®) SPC for further information on dosing

Capecitabine

Capecitabine investigational product is available as 150 mg and 500 mg film-coated tablets.

Capecitabine (total dose of 2000 mg/m^2 daily, in 2 approximately evenly divided doses) will be self-administered orally by patients, starting with Cycle 1/Day 1. Doses are to be taken daily on Days 1 to 14 of each 21-day cycle. Capecitabine should be taken with water within 30 minutes after a meal.

During treatment with lapatinib plus capecitabine, patients should be monitored for conditions that may require dose to be held or discontinued, as described in Appendix 2. Careful attention should be paid to the onset of diarrhea or hand-foot syndrome in particular, and early dose adjustment or prophylactic therapy should be implemented as described in Appendix 2.

Daily dosing of lapatinib plus capecitabine should continue until a criterion for treatment withdrawal or study withdrawal is met (see Sections 10.1 and 10.2, respectively).

Refer to the capecitabine (Xeloda®) US Package Insert and/or the SPC for further information on dosing.

6.1.3 Dose Adjustment

Investigational product dose adjustment and/or discontinuation should be performed according to Appendix 2 and Section 10.1.

Recommended dose reductions for the -1 and -2 dose levels of neratinib are listed in Table 2.

Table 2. Dose Reduction Levels for Neratinib-Related Toxicity

Dose Level	Neratinib
Starting Dose	240 mg
-1	160 mg
-2	120 mg

Recommended dose reductions for the -1 and -2 dose levels of capecitabine in combination with neratinib are listed in Table 3.

Table 3. Dose Reduction Levels for Capecitabine-Related Toxicity (When Administered in Combination with Neratinib)

Dose Level	Capecitabine (administered in combination with neratinib)
Starting Dose	1500 mg/m^2, 750 mg/m^2 BID
-1[a]	1100 mg/m^2, 550 mg/m^2 BID
-2[a]	750 mg/m^2, 375 mg/m^2 BID

Abbreviation: BID: twice daily
[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) (to 75% [level -1] or 50% [level -2] of the starting dose) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

The recommended dose reduction for the -1 dose level of lapatinib is listed in Table 4. Lapatinib doses should be held in patients with an LVEF that is Grade ≥2 and in patients with an LVEF that decreases below the institution's lower limit of normal (LLN; <50% if not specified). Lapatinib (in combination with capecitabine) may be restarted at a reduced dose of 1000 mg/day after a minimum of 2 weeks, if the LVEF recovers to normal and the patient is asymptomatic.

Lapatinib doses should be held in patients with Grade ≥2 NCI CTCAE toxicity, until the toxicity improves to Grade ≤1; lapatinib may be restarted at 1250 mg/day. If the toxicity recurs, then lapatinib (in combination with capecitabine) should be restarted at a reduced dose of 1000 mg/day.

Table 4. Dose Reduction Levels for Lapatinib-Related Toxicity

Dose Level	Lapatinib
Starting Dose	1250 mg
-1	1000 mg (750 mg for severe hepatic impairment; see Appendix 2)

Recommended dose reductions for the -1 and -2 dose levels of capecitabine in combination with lapatinib are listed in Table 5.

Table 5. Dose Reduction Levels for Capecitabine-Related Toxicity (When Administered in Combination with Lapatinib)

Dose Level	Capecitabine (administered in combination with lapatinib)
Starting Dose	2000 mg/m^2, 1000 mg/m^2 BID
-1	1500 mg/m^2, 750 mg/m^2 BID
-2	1000 mg/m^2, 500 mg/m^2 BID

Abbreviation: BID: twice daily

If doses of investigational product are held, study procedures for that cycle will proceed on schedule as planned, without any delay. This also applies to tumor assessments, which should continue to be done every 6 weeks, starting from the first dose of investigational product until the first planned tumor assessment at 6 weeks (±3 days), and then after every subsequent 6 weeks (±3 days) of treatment regardless of any changes in dose or occurrence of AEs. Missed dose(s) of investigational product (i.e., any dose that is not administered within the protocol-defined administration window) will not be made up. The dose adjustment guidelines represent the minimum set of measures that Investigators must follow. However, additional measures may be taken, as necessary, for certain patients per the Investigator's medical judgment. All dose modifications/adjustments should be documented in the patient's source file.

Once an investigational product dose has been reduced for a patient, all subsequent cycles must be administered at that dose, unless further dose reduction is required. Dose re-escalation is not permitted.

Patients must discontinue an investigational product if a criterion for investigational product withdrawal is met (see Section 10.1 and Appendix 2).

Once an investigational product has been discontinued, patients who had been receiving combination therapy may continue to receive the other investigational product as monotherapy, at the Investigator's discretion. This is applicable to both treatment arms of the study. Reintroduction of the discontinued investigational product at a later time during the active treatment phase is not permitted.

Detailed rules for dose adjustments of neratinib, lapatinib, and capecitabine in case of toxicity are provided in Appendix 2.

6.2 Packaging, Labeling and Storage

Detailed packaging information for all investigational products is available in a study reference manual(s). All investigational products will be labeled according to local regulations.

The Sponsor will supply all investigational products (as required), which should be stored at the study sites in a secure location with limited access.

All investigational products should be stored at 25°C (77°F) or below; do not freeze. Excursions are permitted to 30°C (86°F). Neratinib should be stored with desiccant. Keep containers closed tightly.

6.3 Drug Accountability

The study site must maintain accurate records documenting dates and quantities of investigational product received from the Sponsor. On a per patient basis, records must be maintained documenting dates and quantities of investigational product dispensed and returned at each study visit. Any investigational product accidentally or deliberately destroyed must be documented.

Throughout the study, reconciliation will be made between the amount of investigational product supplied, dispensed, returned, and subsequently destroyed or returned to Sponsor. All investigational products that were supplied by the Sponsor will be returned to Sponsor or its representative, or destroyed at the site in accordance with Sponsor guidelines.

Individual patient dosing compliance should be reviewed at each study visit by study site staff. If patient non-compliance is noted, the patient should be re-instructed regarding proper dosing procedures in order to continue in the study. If repeated non-compliance is noted, additional steps may be taken, including withdrawal of the patient from the study (see Section 10.2).

7 CONCOMITANT TREATMENT

All concomitant treatments, therapies and medications will be captured from the signing of the ICF until the end of the treatment. This will include the start date, stop date, generic name, route of administration, dose and indication for treatment.

At screening, patients will be asked what medications they have taken during the last 30 days, which medications are ongoing at the time of screening, any medical conditions that require medication, and all prior cancer therapies. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

7.1 Required Concomitant Treatment

7.1.1 Loperamide Antidiarrheal Therapy

Diarrhea is the major dose-limiting toxicity of neratinib with onset typically occurring early in the course of treatment (during the first few weeks of treatment). Primary prophylactic use of antidiarrheal medication is **mandatory** for all enrolled patients in the neratinib treatment arm. Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is proposed, this should be discussed with the Medical Monitor and the reason documented in the source documents. Second-line antidiarrheal treatments and adjunctive therapies (i.e., octreotide [SANDOSTATIN®]) (or equivalent as approved by the Sponsor) are also recommended for use when appropriate.

The Investigator must review with the patient the **Patient Instructions** for the management of diarrhea and the **Patient Diary** for the patient's daily recording of investigational product during the first 2 cycles, number of stools, and use of loperamide and/or other anti-diarrheals for patients in the neratinib treatment arm. Both the patient and the Investigator must sign the patient instructions for the management of diarrhea. The Patient Instructions and Patient Diary are to be handed to the patient before leaving the site with investigational product on or before Cycle 1/Day 1, with clear instructions to contact the Investigator in the event of *de novo* onset or persistent Grade ≥2 diarrhea to discuss the appropriate course of treatment. The Investigator must also complete and sign the **Investigator Checklist** on or before Cycle 1/Day 1.

Documentation of any occurrences of stools or diarrhea must be as precise as possible and captured in the Patient Diary. For AE recording, documentation of "Intermittent" events of diarrhea is limited to Grade 1. If events of Grade 1 diarrhea are separated by 3 days without any diarrhea, then each event must be documented as separate AEs with corresponding start and stop dates.

The entries on the Patient Diary should be reviewed together with the patient for the first 2 cycles. If the patient has experienced diarrhea since the last visit, details of the daily number of

stools provided on the diary help to grade the diarrhea as precisely as possible (per NCI CTCAE v.4.0). Also, the daily dose of loperamide (or other anti-diarrheals, if applicable) noted on the diary for patients in the neratinib treatment arm will be reviewed and recorded on the CRF.

Loperamide will be dispensed directly by the site on or before Cycle 1/Day 1 with neratinib. It is very important to initiate treatment with loperamide concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

Prophylactic dosing instructions (Cycle 1)

- Inform patients that they will experience diarrhea while taking neratinib.
- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 2 mg (1 tablet/capsule) every 4 hours for the first 3 days. After the first 3 days, take loperamide 2 mg every 6 to 8 hours until the end of the first cycle of therapy regardless of whether the patient is experiencing diarrhea or not.
- For patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) on loperamide, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by Sponsor).
- For Grade 2 diarrhea during Cycle 1 (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection 3 times a day, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by intramuscular injection (equivalent medication may be used with approval of the Sponsor).
- The sites must contact the patient by phone at 1 day, 2 days, and 3 days after the first dose of neratinib to inquire about any diarrhea.

(These phone calls are mandatory and must be recorded in the study chart together with response from the patient and action taken.)

- Instruct patients to promptly report diarrhea symptoms.
- Instruct patient to record the number of stools per day (see Patient Diary, Section 8.5) and the dose of anti-diarrheal medication taken each day (for patients in the neratinib treatment arm) for the first 2 cycles.

For new onset uncomplicated Grade 1 or Grade 2 diarrhea (Cycle 2 and beyond)

Dietetic measures

- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.

- Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.

Pharmacological Treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours.
- For patients with persistent Grade 1 diarrhea on loperamide, Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by the Sponsor).
- For Grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short-acting) 150 µg SC three times daily (TID); or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscular (IM) (equivalent medication may be used with approval of the Sponsor).

For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia)

Dietetic measures (same as above)

Pharmacological treatment

- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).
- Administer octreotide (100-150 µg SC BID or intravenously (IV) (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID).
- Use IV fluids as appropriate.
- Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.

Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 4 neutropenia) per the Investigator's discretion. Results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella,* and *Shigella* testing, when performed, should be reported using the appropriate CRF.

Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction.

7.2 Permitted Concomitant Treatment

Any palliative and/or supportive care for cancer-related symptoms, which are not otherwise specified in the list of prohibited medications (Section 7.3), or drugs with potential for drug-drug interactions (Section 7.4), or in the associated Appendices (Appendix 4, Appendix 5, and Appendix 6), is permitted at the Investigator's discretion.

Specifically, the following treatments are permitted during the study:

- Standard therapies for preexisting medical conditions, medical and/or surgical complications and palliation. All medication(s) as well as previous hormonal therapy, dose and length of therapy should be recorded in the CRF.
- **Bisphosphonates**, regardless of indication, provided patients have been on stable doses for at least 2 weeks prior to enrollment. The stable dose should be maintained during the investigational product treatment period. Patients requiring initiation of bisphosphonate treatment during the course of the study should be discontinued due to progressive disease (PD), unless disease progression can be completely ruled out and clearly documented in the patient's source documentation.
- **Secondary prophylactic use of growth factors** (e.g., granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) may be implemented per the American Society of Clinical Oncology guidelines at the Investigator's discretion, if significant neutropenia or febrile neutropenia/infection is observed.

7.3 Prohibited Concomitant Treatment

The following treatments are prohibited throughout the duration of the active (treatment) phase of the study:

- Any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents, megestrol and hormonal agents.

7.4 Potential for Drug-Drug Interactions

Patients should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the active phase of the study. Patients should also avoid grapefruit/grapefruit juice and herbal remedies, including St John's Wort. Refer to

Appendix 4 for a list of inhibitors and inducers of CYP isoenzymes. If unavoidable, patients taking such agents should be monitored closely.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to lapatinib. Concomitant treatment with strong inhibitors of CYP3A4 should be avoided due to risk of increased exposure to lapatinib. Coadministration of lapatinib with orally administered medicines with narrow therapeutic windows that are substrates of CYP3A4 (e.g., cisapride, pimozide and quinidine) and/or substrates of CYP2C8 (e.g., repaglinide) should be avoided.

Clinically significant drug-drug interaction between sorivudine and 5-fluorouracil (5-FU), resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy. Interactions with allopurinol have been observed for 5-FU that may result in possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. If unavoidable, patients taking such agents should be monitored closely. Steroids given for physiological replacement, as anti-emetics, or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares, are allowed.

Patients using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECG) at the Investigator's discretion. Refer to Appendix 6 for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing Torsade de Pointes (TdP).

Patients taking digoxin, a P-glycoprotein (P-gp) substrate with a narrow therapeutic window, should be monitored closely. The digoxin dose should be adjusted as needed, since neratinib and lapatinib are inhibitors of P-gp. Co-administration of neratinib or lapatinib with digoxin could result in increased digoxin levels and associated digoxin toxicity. Refer to Appendix 5 for a list of substrates and inhibitors of P-gp.

In addition to CYP3A4 and P-gp, lapatinib inhibits CYP2C8 in vitro at clinically relevant concentrations.

Patients taking oral coumarin-derivative anticoagulants (i.e., warfarin and phenprocoumon) should be monitored closely and their anticoagulant dose adjusted as needed.

Patients taking concomitant capecitabine and phenytoin should be carefully monitored. The phenytoin dose may need to be reduced, as some patients receiving both drugs had toxicity associated with elevated phenytoin levels.

The solubility of lapatinib is pH-dependent; thus, concomitant treatment with substances that increase gastric pH (e.g., esomeprazole, lansoprazole) should be avoided, as lapatinib solubility and absorption may decrease.

8 EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Assessment

8.1.1 Clinical Endpoints and Definitions

There are 2 co-primary endpoints in this study: independently-adjudicated PFS and OS. All patients randomized will be evaluated.

The secondary efficacy endpoints include Investigator-assessed PFS, ORR, DOR, and CBR (CR, PR or SD ≥24 weeks), time to intervention for symptomatic metastatic CNS disease, and health outcomes assessments.

Progression-free Survival

Progression-free survival is determined programmatically from adjudicated PD, defined as the interval from the date of randomization until the first date on which recurrence, progression (per RECIST v1.1 [Appendix 7]) or death due to any cause, is documented, censored at the last assessable evaluation, or at the initiation of new anticancer therapy. It is not necessary to confirm disease progression.

Overall Survival

Overall survival is defined as the time from randomization to death due to any cause.

Objective Response Rate

The ORR is defined as the proportion of patients demonstrating either a CR or PR per RECIST v1.1 (Appendix 7) as their best overall response during the study. It is not necessary to confirm response.

Duration of Response

The DOR is measured from the time at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date on which recurrence or PD or death is objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment, per RECIST v1.1 (Appendix 7). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Clinical Benefit Rate

The CBR is defined as the proportion of patients who achieved overall tumor response (CR or PR) or SD for at least 24 weeks. Stable disease is measured from enrollment until the criteria for disease progression or response are met, per RECIST v1.1 (Appendix 7).

Time to Intervention for Symptomatic CNS Disease

Time to intervention for symptomatic metastatic CNS disease is defined as the date of initiation of intervention or therapy for symptomatic CNS disease determined by the investigator to be due to CNS metastasis. This may include brain, leptomeningeal and epidural metastases including epidural spinal cord compression arising from tumor growth in the epidural space.

8.1.2 Tumor Assessments

Tumor assessments will be performed in accordance with the Schedule of Procedures (Appendix 1). Computerized tomography (CT), magnetic resonance imaging (MRI) and other forms of baseline tumor assessments must be performed within 28 days prior to randomization. Tumor assessments will be performed every 6 weeks from the first day of study treatment (Cycle 1/Day 1).

For patients who end therapy for any reason other than radiologically documented progression, every effort should be made to perform radiological tumor assessment until radiologic progression is documented.

Tumor scans and other appropriate tumor assessments must be obtained prior to the start of the next treatment cycle. Overall response will be determined by the Investigator at each visit according to RECIST v1.1 (Appendix 7).

8.1.2.1 *General Information*

All target and non-target sites of disease (see Appendix 7) identified at screening must be followed for the duration of the study. Their presence and absence should be noted throughout follow-up. Overall response for each patient is based on the combined results of target and non-target lesions and the presence or absence of new lesions.

Tumor-based efficacy endpoints (i.e., PFS and ORR) will be based on tumor assessments, which are performed by the Investigators. Response and progression will be evaluated using RECIST v1.1 (Appendix 7).

Tumor assessments will be performed for all patients at 6-week intervals throughout the active treatment phase, starting from Cycle 1/Day 1 until documented disease progression, death, or withdrawal of consent, regardless of whether the patient is continuing or has discontinued study treatment. Additional tumor evaluations will be performed as clinically indicated. Missed tumor assessments must be performed as soon as possible. As soon as evaluations for each tumor assessment are completed, the Investigator should assess the patient's overall response (target plus non-target lesions) based on criteria and overall response algorithms as defined in RECIST v1.1 (Appendix 7). Scans (and/or good color photographs with a ruler for skin lesions) must be assessable for all evaluations.

The longest diameters (LD) for all non-nodal target lesions and the short axis diameter (SAD) of nodal target lesions will be recorded. The LD for all non-nodal target lesions and the SAD of nodal target lesions will be added and reported as the baseline sum longest diameter (SLD). Per RECIST v1.1, for determining CR or PR, all post-baseline tumor measurements will be compared with the baseline SLD; for determining PD, the post-baseline measurement is compared with the smallest SLD recorded since initiation of treatment, including baseline (see Appendix 7).

Patients who discontinue study treatment for reasons other than PD per RECIST will continue to be followed up by protocol for scheduled tumor assessments until PD, and long-term for OS (see Section 10.3).

For patients who show a CR on one scan and on a confirmatory scan obtained 6 weeks later, the frequency of subsequent scans may be reduced at the discretion of the investigator to no less than one scan every 12 weeks.

The same method of measurement (CT/MRI) and the same technique of assessment should be used to characterize each identified and reported lesion from baseline through the final visit. All measurements should be taken and recorded in metric notation, using a ruler or calipers. The screening CT/MRI must be performed within 28 days prior to randomization, and preferably no more than 28 days before the initiation of treatment. As often as possible, lesions should be assessed by the same Investigator using the same method of measurement. Physical examination may not be the sole method of assessment for a solitary lesion.

8.1.2.2 *Computerized Tomography and Magnetic Resonance Imaging*

Computerized tomography and MRI are the recommended methods to measure target lesions selected for response assessment. Conventional CT and MRI 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. The size of CT/MRI scan interval cuts must not change for a patient after screening.

Computerized tomography scans of the chest, abdomen and/or pelvis should be obtained as clinically indicated. Alternatively, CT scans of the chest and separate CT scans of the abdomen and/or pelvis may be obtained. Radiographs may be used during the study to follow lesions seen on a bone scan and confirmed by radiographs at screening. In cases of CT contrast media allergy or renal insufficiency (creatinine >2 mg/dL [176.8 μmol/L]), in which CT scans with contrast cannot be done, enhanced MRIs (for pelvis or abdomen) or CT without contrast (for chest) may be used instead, but the same method of assessment must be used throughout the course of the study. Ultrasound should not be used for the purposes of measuring or evaluating tumors in this study.

Definitions of measurable disease and measurable lesions, documentation of "target" and "non-target" lesions and evaluation of response are summarized in RECIST v1.1 (Appendix 7).

8.1.2.3 *Caliper measurement by clinical examination when lesions are superficial*

Skin lesions that can be measured with calipers as defined in RECIST v1.1 (Appendix 7) or documented using color photography (with ruler) can be considered target or non-target lesions. Skin lesions which cannot be measured with calipers or documented using color photography (with ruler) should be recorded as non-measurable. Otherwise, this clinical measurement should be recorded in the CRF. Documentation by color photography in good light and including a ruler to estimate the size of the lesion is required, and will be provided to the central review vendor for independent evaluation by an oncologist.

Note that when lesions can be evaluated both clinically and radiographically, the radiologic imaging evaluation (by CT or MRI as appropriate) should take precedence.

8.2 Safety Assessment

Refer to the Schedule of Procedures (Appendix 1) for time points. Safety will be assessed with the following procedures: medical history, AEs, vital signs, detailed/brief (system-guided) physical examinations, 12-lead ECGs, LVEF (ECHO or MUGA), and laboratory evaluations.

Adverse events will be graded according to the NCI CTCAE v.4.0. Serious adverse events will be reported until 28 days after the last dose of the investigational product and will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of an SAE occurring any time after the reporting period, it must be promptly reported. More details on AEs can be found in Section 13.

The Patient Diary will be used for recording investigational product intake during the first two cycles. In the case of diarrhea, it also serves to document the number of stools per day and use of loperamide/other antidiarrheal treatments taken.

8.2.1 Laboratory Assessments

Laboratory testing will be performed in accordance with the Schedule of Procedures (Appendix 1).

The institutional laboratory will analyze all hematology, routine blood chemistry and urine samples collected. Samples will be analyzed at a facility meeting Good Laboratory Practice requirements and using methods documented in a methods validation report.

Screening laboratory results may be accepted as the baseline assessment if they are performed within 72 hours before randomization and there are no clinically significant findings.

Laboratory assessments are summarized in Table 6.

Tumor testing for HER2 gene amplification or overexpression will be determined by a central laboratory using the methods presented in Section 8.2.1.1. Wherever possible, tumor tissue from a metastatic site or at or beyond the time of recurrence should be submitted. If the tissue is not available or acceptable, a fresh tumor biopsy may be performed.

Table 6. Laboratory Assessments

Hematology:	Differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils)	
	Hematocrit (Hct)	
	Hemoglobin (Hb)	
	Mean corpuscular hemoglobin (MCH)	
	Mean corpuscular hemoglobin concentration (MCHC)	
	Mean corpuscular volume (MCV)	
	Platelet count	
	Red blood cell (RBC) count	
	Red blood cell distribution width (RDW)	
	White blood cell (WBC) count, with differential	
Coagulation factors:	International Normalized Ratio (INR)	
	Prothrombin time (PT)	
	Activated partial thromboplastin time (aPTT)	
Clinical chemistry:	Albumin	Lactate dehydrogenase (LDH)
	Alkaline phosphatase	Magnesium
	Alanine aminotransferase (ALT)	Phosphorus
	Aspartate aminotransferase (AST)	Potassium
	Bicarbonate	Sodium
	Blood urea nitrogen (BUN)	Total bilirubin
	Calcium	Total protein
	Chloride	
	Serum Creatinine	
	Glucose	
Urinalysis (dipstick; microscopic examination if abnormal):	Blood	
	Protein	
	Glucose	
Serum pregnancy test:	In women of child-bearing capacity (screening only)	
Biomarkers:	HER2 overexpression by IHC and gene amplification by FISH if required for confirmation (see Section 8.2.1.1)	
	ER and PR expression	

All laboratory tests that result in clinically important abnormal results that occur during the study will be repeated at appropriate intervals, until results return either to baseline or to a level deemed acceptable by the Investigator and the Sponsor's medical monitor (or his/her designated representative), or until a diagnosis that provides an explanation is made.

Criteria for reporting abnormal laboratory values as AEs are summarized in Section 13.1.2.

The total volume of blood collected from each patient during the course of the study will be dependent upon the number of treatment cycles a patient completes. Approximately 17 mL of blood will be collected during screening and 15 mL of blood will be collected at subsequent visits (plus 6 mL at each of two visits during Cycle 1 if PK samples are collected).

8.2.1.1 *Immunohistochemistry and Fluorescence In Situ Hybridization Testing of HER2 and ER/PR Status*

Tumor samples will be evaluated for HER2 expression by IHC (HercepTest™) and if required for gene amplification by FISH analysis (IQFISH pharmDx™) as below.

- If IHC 3+, no further testing required to confirm HER2+ status.
- If IHC 2+, further testing required by FISH to confirm HER2+ status.
- If IHC 0 or 1+, sample is considered negative for HER2 status and no further testing will be conducted.

Either primary breast cancer tissue (e.g., from prior surgical resection) or other breast cancer-containing tissue (e.g., from biopsy or excision of cancer-containing lymph node or metastatic lesion) is acceptable for central HER2 testing. Further, breast cancer-containing specimens submitted for central HER2 testing may have been obtained at any time in the patient's breast cancer treatment history, including the period before the development of metastatic disease. Wherever possible tissue from the time of recurrence or metastasis should be submitted.

If there is not enough tissue available, and the IHC result is 2+ and there is no FISH result, or the IHC and FISH both fail to give a result, the site will be asked to ship another sample for re-testing.

Patients may have a fresh tissue biopsy in order to assess eligibility if there is no available tissue for central HER2 testing or if the available tissue (regardless of whether from primary lesion or metastatic site, and regardless of when it was obtained in their disease course) cannot be confirmed to have been fixed with formalin as the fixative.

ER/PR status will be determined using a pharmDx™ kit.

8.2.2 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Appendix 1):

- Blood pressure (systolic and diastolic; mmHg).
- Resting heart rate (beats per minute).
- Body temperature (°C or °F; oral, core [rectal], axillary or tympanic).
- Weight.
- Height (screening only).

Vital signs will be measured after resting in a seated position for 5 minutes.

8.2.3 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Appendix 1).

A full physical exam will be performed at screening. Detailed/brief (system-guided) physical examinations will be done at subsequent time points to evaluate any clinically significant abnormalities, including worsening of conditions included in the patient's medical history.

8.2.4 Electrocardiograms

Single standard 12-lead digital ECGs will be performed in accordance with the Schedule of Procedures (Appendix 1).

The ECG (measured after resting in a supine position for 5 minutes) will include heart rate, rhythm and RR, PR, QRS, and QTc intervals. The ECG will be read and interpreted at the investigational site for patient safety monitoring and documentation will be stored with the source documents.

8.2.5 Left Ventricular Ejection Fraction (LVEF)

Multiple-gated acquisition scan or ECHO scans to determine LVEF will be performed in accordance with the Schedule of Procedures (Appendix 1).

Screening ECHO/MUGA scans must be performed within 28 days prior to randomization.

It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each relevant time point for each patient.

8.3 Other Assessments

8.3.1 Pharmacokinetics

At selected study centers, PK samples will be collected from approximately 100 patients in the neratinib plus capecitabine arm (Arm A) on Days 1 and 15 of Cycle 1, as noted in the Schedule of Procedures (Appendix 1). Patients should be instructed to report the exact time that the dose of neratinib was taken on the days of PK sample collection.

8.3.2 Health Outcomes Assessments

The following health outcomes assessments will be completed by patients, as noted in the Schedule of Procedures (Appendix 1):

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), version 3 (Appendix 8)
- EORTC QLQ-BR23 (breast cancer-specific questionnaire; Appendix 9)
- EuroQol (EQ-5D-5L) multi-dimensional health status questionnaire (Appendix 10)

8.3.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed in accordance with the Schedule of Procedures (Appendix 1). The ECOG categories are summarized in Appendix 3.

Screening ECOG performance status may be accepted as the baseline status if the assessment was performed within 72 hours before randomization and there are no clinically significant findings.

8.4 Protocol Deviations

Protocol deviations should be reported to the Sponsor (or designee).

8.5 Patient Diary

The Patient Diary used for recording of investigational product intake during the first 2 cycles. The number of stools per day will also be recorded on the Patient Diary for the first 2 cycles. In addition, patients in the neratinib treatment arm will record the use of loperamide/other antidiarrheal treatment taken along with the dose of neratinib for the first 2 cycles.

9 STUDY CONDUCT

A Schedule of Procedures is provided in Appendix 1.

In addition to the procedures listed below, unscheduled clinic visits and procedures should be performed at the Investigator's discretion to assess symptoms and concerns newly reported by the patient to rule out or confirm potential recurrence, or for the purpose of assessing the patient's safety.

9.1 Screening/Baseline

Screening activities are to be conducted within 21 days prior to randomization. Baseline assessments must be done within 72 hours before randomization. Randomization should occur after all baseline assessments have been completed and the site confirms that the patient still meets all eligibility requirements.

The following information and assessments will be performed, collected and/or recorded at screening in accordance with the Schedule of Procedures (Appendix 1):

- Signed ICF for the study.
- Collect demography: date of birth, sex, race (Asian, Black or African American, White, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, Other), and ethnicity (Hispanic or Latino, Non-Hispanic or Non-Latino).
- Medical history:
  - Record chronic conditions and/or medical history of significance (including the review of history of cardiac, pulmonary and gastrointestinal disease), relevant surgical procedures and symptoms experienced during the previous 30 days as well as those ongoing at the time of screening, and any medical conditions that require medication.
  - Cancer history, including but not limited to: date of first diagnosis, nodal status (based on pathologic assessment of nodes at the time of surgery, either before adjuvant chemotherapy or after completion of neoadjuvant chemotherapy), histology, tumor stage at diagnosis, predictive and prognostic biomarkers, previous chemotherapy/biotherapy/ immunotherapy, previous adjuvant therapy (drug names, start and stop dates, reason for TD), previous radiation, and prior cancer-related surgical therapies.
  - Other previous and concomitant medication will be documented, as described in Section 7.
- Physical examination. Refer to Section 8.2.3.

- Vital signs, height and weight. Refer to Section 8.2.2.
- ECG. Refer to Section 8.2.4.
- LVEF (ECHO or MUGA). Refer to Section 8.2.5.
- ECOG performance status. Refer to Section 8.3.3.
- Serum pregnancy test. Refer to Section 8.2.1.
- Laboratory tests (urine dipstick, hematology and serum chemistry panel). Refer to Section 8.2.1.
- Radiographic (or other appropriate modality for) tumor assessment (RECIST v1.1). Refer to Section 8.1.2.
- In addition, following signing of informed consent, tumor tissue must be prepared and sent for central laboratory confirmation of HER2 expression and hormone receptor status (Refer to Section 8.2.1.1).

The following assessments will be performed at baseline in accordance with the Schedule of Procedures (Appendix 1):

- Physical examination. Refer to Section 8.2.3.
- Vital signs, height and weight. Refer to Section 8.2.2.
- ECOG performance status. Refer to Section 8.3.3.
- Health outcomes assessments. Refer to Section 8.3.2.
- Laboratory tests (urine dipstick, hematology and serum chemistry panel). Refer to Section 8.2.1.

9.2 Active Treatment Phase

Neratinib (Arm A) or lapatinib (Arm B) will be self-administered by patients once daily during each 21-day cycle. Capecitabine will be self-administered by patients BID on Days 1 to 14 of each 21-day cycle (Arm A and B).

The following will be performed during the active treatment phase in accordance with the Schedule of Procedures (Appendix 1):

- Physical examination. Refer to Section 8.2.3.
- Vital signs and weight. Refer to Section 8.2.2.

- ECG. Refer to Section 8.2.4.
- LVEF. Refer to Section 8.2.5.
- ECOG performance status. Refer to Section 8.3.3.
- Health outcomes assessments. Refer to Section 8.3.2.
- Concomitant medication assessment. Refer to Section 7.
- Adverse event assessment. Refer to Section 13.
- Laboratory tests (hematology and serum chemistry panel). Refer to Section 8.2.1.
- Radiographic (or other appropriate modality for) tumor assessment. Refer to Section 8.1.2.
- Dispense investigational product. Refer to Sections 6.1.
- Review the Patient Instructions for the management of diarrhea with the patient and dispense antidiarrheal medication. Refer to Section 7.1.1.
- Review entries in the Patient Diary through Cycle 2. Refer to Section 8.5.
- Treatment compliance assessment. Refer to Section 6.3.
- PK sampling. Refer to Section 8.3.1.

9.3 Treatment Discontinuation Visit

The TD visit will be used to perform safety assessments and should be completed within 3 days after the last dose of investigational product.

The following will be performed in accordance with the Schedule of Procedures (Appendix 1):

- Physical examination. Refer to Section 8.2.3.
- Vital signs and weight. Refer to Section 8.2.2.
- ECG. Refer to Section 8.2.4.
- LVEF. Refer to Section 8.2.5.
- ECOG performance status. Refer to Section 8.3.3.
- Health outcomes assessments. Refer to Section 8.3.2.
- Concomitant medication assessment. Refer to Section 7.
- Adverse event assessment. Refer to Section 13.
- Laboratory tests (hematology and serum chemistry panel). Refer to Section 8.2.1.

- Treatment compliance assessment. Refer to Section 6.3.

Patients who remain on study will enter the long-term follow-up phase after the TD visit. Adverse events will continue to be monitored until the 28th day after the last dose of investigational product.

If a patient discontinues from the study for a reason other than disease progression or withdrawal of consent, he/she will continue CT/MRI assessments every 6 weeks, starting from Cycle 1/Day 1.

9.4 Safety Follow-up Contact

Patients will be contacted by phone 28 days (+5 days) after the last dose of investigational product to collect AE, cancer therapy (anti-cancer medication, cancer-related radiotherapy, and cancer-related surgery), concomitant medication, and survival information.

9.5 Long-term Follow-up Phase

Patients who discontinue study therapy will be followed for survival status during the long-term follow-up phase. If a patient discontinued study therapy due to toxicity, tumor assessments will continue to be performed at 6-week intervals throughout the long-term follow-up phase, until documented disease progression, death, or withdrawal of consent. Patients will also be contacted every 12 weeks for survival status and to collect the following data:

- Anti-cancer medications, including dose and regimen, taken since last contact.
- Cancer-related radiotherapy administered since last contact.
- Cancer-related surgeries/procedures performed since last contact.

The long-term follow-up phase will continue until patient death or withdrawal of consent. Survival follow-up will occur via telephone call if the site is unable to confirm status via chart review.

If a patient withdraws from the long-term follow-up phase of the study, attempts should be made to contact the patient to determine the reason(s) for discontinuation (see Section 10.3).

Patients who are no longer continuing with scheduled study visits will be followed for SAEs until the patient starts a subsequent cancer therapy (see Section 13.3).

9.6 End of Study

The EOS will occur as of the date of the last visit of the last patient undergoing the study. In the event that the EOS is declared earlier, investigational product(s) will be available to patients who continue to receive clinical benefit as described in Section 4.1.

10 PATIENT WITHDRAWAL AND REPLACEMENT

10.1 Investigational Product Discontinuation

Withdrawal due to an AE should be distinguished from withdrawal due to other causes and recorded on the appropriate AE CRF page.

If one of the two investigational products given in combination has been discontinued, patients may continue to receive the other investigational product as monotherapy, at the Investigator's discretion. This is applicable to both treatment arms of the study. Reintroduction of the discontinued investigational product at a later time during the active treatment phase is not permitted.

Patients **must** be discontinued from **investigational product(s)** (but may remain in the study, if appropriate) under the circumstances listed below and in Appendix 2, unless otherwise agreed with the Medical Monitor.

- If the patient requires more than two dose reductions of the investigational product(s) (see Appendix 2).
- If investigational product(s) is withheld due to an AE for >28 days.
- Disease progression.
- Initiation of alternative anti-cancer therapy. Any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents, megestrol and hormonal agents are prohibited (see Section 7.3).
- Pregnancy (see Section 13.4).
- Investigator request.
- Patient request (i.e., withdrawal of consent for treatment).

10.2 Withdrawal from the Study

Patients may withdraw from the **entire study, including follow-up,** at any time without penalty and for any reason without prejudice to his or her future medical care. Study withdrawal may occur for the following reasons:

- At the discretion of the Investigator.
- At the patient's request (withdrawal of consent for the study).

- Lost to follow-up (defined as three failed attempts to contact by phone, followed by one attempt by sending a certified letter).
- If the entire study is terminated prematurely as described in Section 11.

A patient may also be withdrawn from **investigational product/study** by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IEC)/IRBs.

10.3 Procedures for Patient Withdrawal

When a patient is withdrawn from the study, the Investigator will notify the Sponsor. In all cases, the reason(s) for premature discontinuation/withdrawal and the primary reason must be recorded on the CRF. If a patient is prematurely withdrawn from the investigational product or the study for any reason, the Investigator must make every effort to perform the evaluations described for the TD visit, the safety follow-up contact 28 days later, and a follow-up visit 12 weeks later. If a patient discontinues due to an AE, he/she should continue to be under medical supervision until symptoms cease or the condition becomes stable.

If a patient withdraws consent but agrees to undergo a final examination, this will be documented on the CRF and the Investigator's copy of the ICF, which will be countersigned and dated by the patient.

If a patient is lost to follow-up or voluntarily withdraws from study participation, every effort should be made to determine why the patient was lost to follow-up or withdrew consent. This information, including the date, should also be recorded on the patient's conclusion of patient participation CRF.

All patients will remain on active study treatment until treatment or study discontinuation, death, or withdrawal of consent. Upon confirmed disease progression, or discontinuation of randomly assigned investigational product for any other reason, all further anti-cancer treatment will be at the Investigator's discretion. All patients will remain in the long-term follow-up phase for survival unless consent has been withdrawn or until death.

10.4 Patient Replacement

Patients will not be replaced.

11 PREMATURE TERMINATION OF THE STUDY

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. Investigational product(s) will be available to patients who continue to receive clinical benefit following the EOS as described in Section 4.1.

If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The Investigator will also return all investigational products, investigational product containers and other study materials to the Sponsor or have them destroyed locally according to Sponsor guidelines. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC and regulatory agency with final reports and summaries as required by regulations. For investigational new drug application studies, the Investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

12 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study. Additional details of the analysis will be provided in a Statistical Analysis Plan (SAP), which will be finalized prior to unblinding the data. Any deviations from the protocol or SAP-specified analyses will be identified in the clinical study report.

A final PFS analysis will be conducted when 419 PFS events have occurred and a final OS analysis will be conducted when 378 deaths have occurred. An interim analysis of OS will be conducted at the time of the final PFS analysis.

12.1 General Considerations

The primary efficacy analysis will be performed on the intent to treat (ITT) population, defined as all patients randomized into the study. Formal definitions of the analyses populations are provided in the SAP.

12.2 Study Patients

12.2.1 Disposition of Patients

The number and percentage of patients entering and completing each phase of the study will be presented, stratified by treatment. Reasons for withdrawal pre- and post-randomization will also be summarized.

12.2.2 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, baseline characteristics including predictive and prognostic biomarkers, concomitant disease, and concomitant medication will be summarized by means of descriptive statistics (n, mean, standard deviation, median, minimum and maximum) or frequency tables, overall and stratified by treatment.

12.2.3 Treatment Compliance

Duration of treatment will be summarized separately for each investigational product by treatment group. In addition, the cumulative quantity, dose intensity (quantity per time unit) and the relative dose intensity (dose intensity/scheduled dose per time unit) will be summarized. The number of patients with dose holds or dose reductions will be tabulated for each investigational product by treatment group.

12.3 Efficacy Analyses

12.3.1 Primary Efficacy Analysis

The co-primary endpoints are independently adjudicated PFS and OS. PFS is defined as disease progression demonstrated by radiographic imaging or other appropriate modality, or death due to any cause. Tumor evaluations will be performed by a central review vendor.

Patients will be stratified at randomization by whether they had 2 or ≥3 prior HER2+ MBC regimens in the metastatic setting, their geographic region (North America vs. Europe including Israel vs. Rest of World), disease category (visceral vs. non-visceral only), and hormone receptor status (ER and/or PR positive vs. ER and PR negative). All efficacy endpoints will be summarized by treatment group and visit when appropriate.

The efficacy assessment in PFS will be assessed by a blinded, independent, central review of tumor assessments for all patients at screening, and then after every 6 weeks from first dose of investigational product, regardless of treatment schedule modification (e.g., dose delay), until documented disease progression or death. PFS will be independently-assessed using RECIST v1.1.

Missed tumor assessments must be performed as soon as possible. Patients who discontinue from study treatment for a reason other than radiographically confirmed (or confirmation by other appropriate modality) objective disease progression will have radiological tumor assessments performed approximately every 6 weeks from the date of the last tumor assessment until documented disease progression or death.

Survival data will be collected throughout the active treatment phase and during the long term follow-up phase. Survival follow-up after patient discontinuation of investigational product will be conducted approximately every 12 weeks to assess for survival until patient's death, withdrawal of consent, or the EOS.

12.3.1.1 *Statistical Methods*

When 419 PFS events have occurred the primary PFS analysis will be performed. The median time to PFS and corresponding two-sided 95% confidence intervals will be calculated using the product limit estimator and displayed using a Kaplan-Meier graph, by treatment group. A log-rank test controlling for hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, visceral disease, and geographic region strata will be used to test the null hypothesis of no difference in the time to PFS between the two treatment groups at the alpha level of 0.01. Subjects who discontinue therapy early will be censored at their last available time point. Sensitivity analyses will be performed to investigate the impact of differential dropout between the two treatment groups on the treatment effect estimate.

When the PFS analysis is performed, an interim analysis will be performed on the OS endpoint. When 378 deaths have occurred, primary OS analysis (final analysis) will be performed. The median time to PFS and corresponding two-sided 95% confidence intervals will be calculated using the product limit estimator and displayed using a Kaplan-Meier graph, by treatment group. A log-rank test controlling for hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, visceral disease status, and geographic region strata will be used to test the null hypothesis of no difference in the hazard between the two treatment groups at the alpha level of 0.002 at the interim analysis and 0.038 for the final analysis.

12.3.2 Secondary Efficacy Analyses

The secondary efficacy endpoints include Investigator-assessed PFS, ORR, DOR, and CBR (CR, PR or SD ≥24 weeks).

The secondary efficacy assessments include:

- The comparison of clinically relevant improvements in breast cancer patients with respect to radiographic changes or changes in other appropriate modalities, including ORR, DOR and CBR (CR or PR or SD ≥24 weeks).
- In addition, time to onset of symptomatic metastatic CNS disease and the quality of life instruments EORTC QLQ-C30, BR23, and EuroQol EQ-5D-5L will be analyzed.

12.3.2.1 *Statistical Methods*

The treatment difference in the secondary efficacy endpoints of ORR and CBR will be analyzed using a Cochran-Mantel-Haenzel (CMH) Chi-square test, stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, geographic region, and disease state (visceral vs. non-visceral only). The treatment difference in the secondary efficacy endpoints of DOR and PFS from Investigator-assessed PD will be analyzed using a product limit estimate of the median time to event. Differences between treatment groups will be examined using a log-rank test statistic stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, visceral disease status, and geographic region strata (similar to the analysis for the primary endpoints). All time-to-event endpoints, including time to intervention for symptomatic CNS disease, will be displayed using a Kaplan-Meier survival plot. Health outcomes assessments (EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-5L) will be analyzed using a random effects mixed model with treatment, time, number of prior HER2-directed regimens in the metastatic setting (binary), geographic region, disease category, and the treatment by time interaction. Endpoints that could be affected by missing values (e.g., health outcomes assessments) will be analyzed using a sensitivity analysis to quantify the impact of missing values in the results.

12.4 Safety Analyses

Patients receiving at least 1 dose of investigational product will be evaluable for safety.

12.4.1 Investigational Product Exposure

Extent of exposure to each investigational product will be summarized by total dose, number of cycles, number of missed doses, number of dose delays, number of dose reductions.

12.4.2 Adverse Events

Safety will be assessed based on medical history, vital sign measurements, physical examination findings, ECG results, MUGA or ECHO, liver function test results, ECOG performance status, and laboratory assessments. Adverse events and SAEs will be reported until 28 days after the last dose of investigational product(s) and will be followed until resolution or until condition stabilizes. Should an Investigator be made aware of any SAE occurring any time after the reporting period, it must be promptly reported.

All safety endpoints will be summarized by treatment group and visit when appropriate. Adverse events and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system v.15 or later and will be tabulated by system organ class (SOC) and preferred term. All AEs will be graded according to the NCI CTCAE v.4.0. Differences in the incidence of the most common AEs and SAEs between the two treatment groups will be investigated using a CMH chi-square test, stratified on hormone receptor status, prior number of HER2-directed regimens in the metastatic setting, geographic region, and visceral or non-visceral only disease.

A patient who experiences the same AE more than once within a SOC or preferred term category will be counted only once, using the worst toxicity grade for that event.

Serious adverse events and deaths will be provided in a listing. Treatment-emergent adverse events (TEAEs) leading to treatment discontinuation, dose modification, dose hold, and/or delay of investigational product will be tabulated by SOC, PT, and treatment group.

12.4.3 Laboratory Results

Laboratory test results will be collected pretreatment and on day 1 of each treatment cycle until the TD visit. Standard reference ranges will be used for missing or discrepant normal ranges.

Mean change from baseline in laboratory test values at each visit will be provided. On-study laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be summarized.

12.5 Other Analyses

12.5.1 PK analysis

A population PK study, with sparse sampling at a subset of study sites, will be included in the study to assess the variability of neratinib concentrations when administered in combination with capecitabine among individuals in the target patient population. Blood samples will be collected as specified in Appendix 1, and they will be processed and stored until analysis.

Concentrations of neratinib will be measured in plasma with a validated assay method. NONMEM, a statistical software program that uses non-linear, mixed effects models to determine PK parameters (clearance and volume of distribution), the inter- and intra-patient variability and the population variability in the parameter estimates will be used for this analysis. Random sources of error, intrinsic factors (e.g., age, sex, race, body weight, liver function and renal function) and extrinsic factors (e.g., capecitabine, diarrhea frequency, smoking status) will be evaluated to identify factors that contribute to the observed variability in the PK parameter estimates.

The concentrations in this study will be used in the development of a structural model, and it will include results from other neratinib studies that included intensive sampling. The best model will be evaluated by goodness of fit statistics, reduction in the objective function and posterior predictive checks.

A population pharmacokinetic-pharmacodynamic analysis of neratinib efficacy and tolerability endpoints will be performed in this patient population. The final PK model will be used to generate post-hoc neratinib patient-level plasma PK profiles, from which patient-level neratinib area under the curve (AUC) and maximum plasma concentration (C_{max}) exposure metrics will be estimated. Neratinib dose and estimated AUC and C_{max} exposure metrics will then be used to complete an exploratory data analysis of potential exposure-response relationships for efficacy and safety endpoints.

12.5.2 Health Outcomes Assessments

Health outcomes assessments will include the EORTC QLQ-C30, EORTC QLQ-BR23 and the EQ-5D-5L. Questionnaires will be completed by patients at time points specified in Appendix 1.

12.6 Interim Analyses

No interim PFS analysis for early stopping is planned. An interim OS analysis will be performed at the time of final PFS analysis.

The Lan-DeMets alpha spending function approach will be used to adjust the O'Brien-Fleming boundary if the timing based on the final PFS analysis does not correspond to the expected information time of half of the OS events (DeMets and Gordon Lan 1994; Cook 2003).

The hazard rate in the control arm for survival will be assessed to determine if the sample size or duration of follow-up or both should be adjusted to ensure timely achievement of the required 378 death events.

12.7 Determination of Sample Size

The co-primary endpoints will be analyzed using an overall Type I error rate of 0.01 for PFS and 0.04 for OS. To detect a hazard ratio (control versus treatment) of 0.70 with approximately 85% power, 419 PFS events (PD/deaths) are required to be observed; this assumes a median (ITT) PFS of 8.0 months (34.7 weeks) for the experimental arm (neratinib plus capecitabine) and 5.6 months (24.3 weeks) for the control arm (lapatinib plus capecitabine). It is expected that the 419th event will be observed at approximately 26 months after the first patient is enrolled, which would correspond to approximately half of the death events needed to be observed. At this time, an interim analysis on OS will also be performed. For the OS endpoint, a group sequential method will be employed to maintain the overall Type I error rate at 0.04. Specifically, O'Brien-Fleming boundaries will be calculated to create appropriate critical values to which the log rank statistic will be compared.

Information Fraction	Expected Death Events	Study Month	Boundary (Reject H_0)	Significance Level
50%	185	26	3.066	0.002
100%	378	50	2.058	0.038

These boundaries are designed to detect a hazard ratio (control versus treatment) of 0.725 with approximately 85% power. Overall, 378 events (deaths) are required to be observed; this assumes a median (ITT) OS of 30.3 months for the experimental arm (neratinib plus capecitabine) and 22.0 months for the control arm (lapatinib plus capecitabine). Approximately 600 patients will be enrolled and randomized equally between the two treatment arms.

13 SAFETY DATA COLLECTION, RECORDING AND REPORTING

All observed or volunteered AEs regardless of treatment group or causal relationship to investigational product will be recorded on the AE page(s) of the CRF.

13.1 Definitions

13.1.1 Adverse Events

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation patient administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product (definition per International Conference on Harmonisation [ICH] E2A and E6 R1).

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology on the AE CRF page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see Section on SAEs) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AE.

TEAEs are those events that occur or worsen on or after first dose of investigational product and up to 28 days after the last dose.

13.1.2 Abnormal Laboratory Results

The criteria for determining whether an abnormal laboratory test result should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or,

- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting and an AE), and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Test result leads to any of the outcomes included in the definition of a SAE, and/or,
- Test result is considered to be an AE by the Investigator or by the Sponsor

Any abnormal test result that is determined to be an error does not require reporting as an AE, even if it did meet one of the above criteria except for when the test result leads to any of the outcomes included in the definition of a SAE. Clinically significant laboratory results must be recorded in the patient's CRF.

13.1.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose (ICH E2A and E6 R1):

- Results in death.
- Is life-threatening.
  This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the SAE definition.

13.1.4 Hospitalization

Any inpatient hospital admission that includes a minimum of an overnight stay to a healthcare facility meets the criteria for 'hospitalization'. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

The following are not considered to be hospitalization:

- Rehabilitation facilities.
- Hospice facilities.
- Respite care (e.g., caregiver relief).
- Skilled nursing facilities.
- Nursing homes.
- Routine emergency room admissions.
- Same day surgeries (as outpatient /same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality).
- Social admission (e.g., patient has no place to sleep).
- Administrative admission (e.g., for yearly physical examination).
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation or the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should

be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

13.1.5 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reactions (SUSAR) are events which are serious as per the above criteria, the nature or severity of which is not consistent with the applicable product information (e.g., current Investigator's Brochure) and are judged by the Investigator or by the Sponsor to be related to investigational product. For a non-Sponsored investigational product (e.g., a comparator product) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/SPC.

13.1.6 Severity Assessment

Adverse events will be graded by the Investigator according to the NCI CTCAE v.4.03 (Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html), according to the following general categories:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it meets one of the criteria for SAEs, listed above.

13.1.7 Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF and report such an assessment in accordance with the serious adverse reporting requirements, if applicable. A

suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (e.g., investigational product or other illness). The relationship of the AE to the study treatment (investigational product, comparator or placebo [as applicable]) will be assessed following the definitions below:

- 'No' (unrelated): Any event that does not follow a reasonable temporal sequence from administration of investigational product AND is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- 'Yes' (related): Any reaction that follows a reasonable temporal sequence from administration of investigational product AND follows a known response pattern to the suspected investigational product AND recurs with re-challenge, AND/OR is improved by stopping the investigational product or reducing the dose.

In addition, if the Investigator determines an AE is associated with study procedures, the Investigator must record this causal relationship on the AE CRF page and report such an assessment in accordance with the SAE reporting requirements, if applicable.

13.1.8 Special Reporting Situations

Safety events of interest on the Sponsor's investigational product that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of an investigational product.
- Suspected abuse/misuse of an investigational product.
- Inadvertent or accidental exposure to an investigational product.
- Medication error that may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength.
- Suspected transmission via an investigational product of an infectious agent.

Special reporting situations should be recorded on the AE CRF page. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE form and reported as required (see Section 13.3).

13.2 Reporting Adverse Events

For serious and non-serious AEs, the reporting period to the Sponsor (or its designated representative) begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through 28 calendar days after the last administration of the investigational product.

For all AEs with causal relationship to the investigational product, follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at the level acceptable to the Investigator, and the Sponsor concurs with that assessment.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

13.3 Reporting Serious Adverse Events

All SAEs, irrespective of relationship to investigational product, must be reported within 24 hours of discovery or notification of the event to the Sponsor or designated representative using the SAE form. The SAE form must be signed by the Investigator. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to follow-up information on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases. For SAE reporting information, please refer to the Study Contact List which is provided as a separate document.

Relevant medical records should be provided to the Sponsor or its designated representative as soon as they become available; autopsy reports should be provided for deaths if available.

Should an Investigator be made aware of an SAE occurring any time after the reporting period, it must be promptly reported.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

13.4 Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate Exposure-In-Utero (EIU) form.

For investigational products and for marketed products used as investigational product in neratinib studies, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed (e.g., environmental exposure) to the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure) for 28 days after last dose of or exposure to investigational product.
- A male partner of a pregnant female has been exposed to the investigational product, either due to treatment or environmental exposure, within 3 months prior to the time of conception and/or is exposed during his partner’s pregnancy (paternal exposure).

If any study patient or study patient’s partner becomes or is found to be pregnant during the study patient’s treatment with the investigational product or exposure as defined above, the Investigator must submit this information on an EIU form to the Sponsor (or its designated representative). In addition, the Investigator must submit information regarding environmental exposure to an investigational product in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU form. This must be done irrespective of whether an AE has occurred and within 24 hours of

awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see following information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (e.g., induced abortion) and then notify the Sponsor or its designated representative of the outcome as a follow-up to the initial EIU form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [including that in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the neonatal death as related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

13.5 Sponsor Reporting Requirements to Health Authorities and IRB/IEC

The Sponsor assumes responsibility for reporting of AEs including SUSARs according to local and international regulations, as appropriate. The Investigator (or the Sponsor where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

14 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

The Sponsor of this study may delegate some administrative aspects of this study to a duly authorized representative including, but not limited to, study initiation, monitoring and management of SAE reports.

14.1 Data Collection, Processing and Monitoring

14.1.1 Case Report Forms and Source Documentation

All data captured for the study is planned to be electronic. However, if necessary, data captured may be performed using paper CRFs.

CRFs will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided by the Sponsor or designated representative.

The Investigator is responsible for maintaining adequate and accurate CRFs which have been designed to record all observations and other data pertinent to the clinical investigation. Each CRF should be filled out completely by the Investigator or delegate as stated in the Site Delegation List.

If paper CRFs are used, then all CRFs should be completed in a neat legible manner to ensure accurate interpretation of the data; a black ball-point pen should be used to ensure the clarity of reproduced copies of all CRFs. Incorrect entries should be crossed with a single line. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary, by an authorized (Investigator/co-worker) person. Overwriting of this information or use of liquid correcting fluid is not allowed.

Once the site monitor has verified the contents of the completed CRF pages against the source data, queries may be raised if the data are unclear or contradictory. These queries must be addressed by the Investigator and verified by the clinical research associate. After all the data issues are resolved, these CRFs may be locked to prevent any further data changes. At the end of the study or prior to the site closeout visit, the Investigator will review and approve the data for completeness and accuracy.

14.1.2 Study Monitoring and Access to Source Documentation

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), other national authorities, and local health authorities, the Sponsor and representatives, and the IRB/ Ethics Committee (EC) for each study site. The Investigator will permit authorized representatives of the Sponsor, the respective national or local health authorities and auditors to inspect facilities and records relevant to this study.

The Sponsor or representative's monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy and consistency of the data; and adherence to local regulations on the conduct of clinical research. Source data to be reviewed and/or during this study will include, but is not restricted to: patient's medical file, patient's diary (if applicable), and original laboratory test, histology and pathology reports. All key data must be recorded in the patient's hospital notes.

Auditors, IEC/IRB and/or regulatory inspectors will also have access to the CRFs and source documents. The ICF will include a statement by which the patient allows the monitor/auditor/inspector from the IEC/IRB or regulatory authority access to source data (e.g., patient's medical file, appointment books, original laboratory test reports, X-rays, etc.) that substantiate information in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal drug information.

14.1.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be convened for this study and will act in an advisory capacity to the Sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and for monitoring the overall conduct of the study. The membership criteria, meeting schedule, and other details of the DMC are described in the DMC Charter.

14.1.4 Data Quality Assurance

During and/or after completion of the study, quality assurance auditor (s) named by the Sponsor or the regulatory authorities may wish to perform on-site audits. The Investigators will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor's representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH Good Clinical Practice (GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6), US Investigational Drugs (21 Code of

Federal Regulations [CFR] 312), EU Clinical Studies Directive (Directive 2001/20/EC), and applicable regional regulatory requirements.

14.1.5 Data Processing

All data will be entered by site personnel into the CRF provided (as detailed in Section 14.1.1).

The data management plan will include specifications for data review and data consistency. Outstanding query reports will be sent to the study monitors for resolution by site personnel.

To minimize sources of bias in this open label study, access to treatment information will be limited to specific site, CRO and Sponsor personnel. All individuals with access to treatment information should not disclose this information to others.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference List (WHODrug), which employs the Anatomical Therapeutic Chemical classification system. Medical history and AEs will be coded using MedDRA terminology. The versions of the coding dictionaries will be provided in the Clinical Study Report.

14.1.6 Retention of Data and Study Records

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, ICFs, laboratory test results, and drug inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by agreement with the Sponsor. The Investigator should obtain written permission from the Sponsor prior to the destruction of any study document.

These records should be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with 21 CFR §312.68 or other National Regulatory Authorities.

14.2 Ethical Aspects

14.2.1 Good Clinical Practice and Ethical Conduct of the Study

This protocol accords with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki) as set forth at the 18th World Medicines Association (Helsinki 1964) and amendments thereto. The most current amended version will be in effect.

The procedures set out in this study protocol are also designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH and in keeping with local legal requirements.

14.2.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from the patient or patient's legal representative. If informed consent has not been obtained, no protocol-required procedures are to be performed on the patient and no patient data are to be transferred to the Sponsor. Documentation of informed consent must be recorded in the source documents for each patient.

The study will be discussed with the patient, and the patient will receive written information and an explanation of what the study involves, i.e., the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. If applicable, the information will be provided in a certified translation of the local language.

A signed, IRB/IEC approved, ICF must be obtained from patient before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record. Signed ICFs must remain in each patient's study file and must be available for verification by study monitors at any time. A copy of the fully signed ICFs will be given to the patient.

If the IEC/IRB requires modification of this form, the documentation supporting this requirement must be provided to the Sponsor, along with the new version. The Sponsor reserves the right to reject these modifications, should they not cover the minimum information required by ICH GCP.

A patient wishing to participate must also must provide Authorization for Use and Release of Health and Research Study Information (US only) or Data Protection Consent (Europe only) prior to any study-related procedures or change in treatment.

If a patient is not physically or mentally competent to understand and to give their informed consent to participate in the study (e.g., is blind or illiterate), a legally acceptable representative or impartial witness, as applicable, may sign the ICF on behalf of the patient. It remains the responsibility of the principal Investigator to assure that the patient is suitable for inclusion in this study and will be able to adhere to all study procedures throughout the course of the study.

The explicit wish of a mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be respected by the Investigator.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

14.3 Other Study Administration Aspects

14.3.1 Protocol Approval and Protocol Amendment

The protocol (approved by the Sponsor or its representative) will be submitted to the IRB/IEC for review and it must be approved before the study is initiated. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

Any change in the study plan requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the patients.

14.3.2 Investigator Responsibilities

The Investigator undertakes to perform the study in compliance with the protocol, ICH Guidelines per GCP and the applicable regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The Investigator should also be able to demonstrate a potential for recruiting the required number of suitable patient within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to the Sponsor (or its representative) before starting the study.

If the patient has a primary physician, the Investigator should, with the patient's consent, inform the primary physician of the patient's participation in the study.

Agreement with the final clinical study report will be documented by the signed and dated signature of the principal or coordinating Investigator in compliance with ICH E3.

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator agreement to confirm acceptance and willingness to comply with the study protocol.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study. In particular, the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/IEC must be informed of study completion.

It is the responsibility of the Investigator to submit this protocol, the final approved informed consent document (approved by the Sponsor or its representative), relevant supporting information, and all types of patient recruitment or advertisement information (approved by the Sponsor or its representative) to the IRB/IEC for review and it must be approved before the study is initiated. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

Investigational product supplies will not be released and the patient recruitment will not begin until this written approval has been received by the Sponsor or its designee.

The Investigator is responsible for keeping the IRB/IEC appraised of the progress of the study and of any changes made to the protocol as deemed appropriate, and at least once a year. The Investigator must also keep the IRB/IEC informed of any serious and significant AEs.

14.3.3 Patient Confidentiality

Data collected during this study may be used to support the development, registration or marketing of neratinib. All data collected during the study will be controlled by the Sponsor (or designee) and the Sponsor will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor and/or the company organizing the research on the Sponsor's behalf to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may additionally be reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number. The results of this study may be used in other countries throughout the world that have ensured an adequate level of protection for personal data.

Written Authorization (United States [US] sites only) or Data Protection Consent (EU sites only) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (e.g., Health Insurance Protection and Portability Act [HIPAA]), European Union Data Protection Directive 95/46/EC ("EU Directive") and any other state and country privacy requirements).

14.3.4 Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in neratinib; any significant equity interest in the Sponsor, as defined in the US CFR (21 CFR 54.2(b)).

In consideration of participation in the study, the Sponsor will pay the Investigator, study site or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

14.3.5 Publication Policy

The Sponsor encourages publication of results derived from the clinical research it sponsors, regardless of outcome. Publications include papers in peer reviewed medical journals, abstract submission with a poster or oral presentation at a scientific meeting, or making results public by some other means. The Sponsor will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-chairs/Principal Investigator(s) are permitted to publish/present the results of the study, in part or in their entirety without the written authorization of the Sponsor. The review is aimed at protecting the Sponsor's pre-existing propriety information and commercial interests.

<u>First Publication</u>

The results of the entire multicenter study shall be presented in a first publication upon completion of the entire multicenter study (data lock), with authorship being determined by the Sponsor using the criteria defined by the International Committee of Medical Journal Editors. At least two Sponsor representatives will also be included as coauthors on the first publication of the results of the entire multicenter study to allow recognition of the Sponsor's involvement in the design and execution of the study.

<u>Subsequent Publications</u>

Results from data subsets should not be published in advance of the first publication, and must make reference to it. Publications must normally include at least two Sponsor authors to allow recognition of the Sponsor's involvement. In all publications, the study is to be identified as PUMA-NER-1301 (NALA), or some other Sponsor-approved and published name.

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16 SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Officer

Title: A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2-Directed Regimens in the Metastatic Setting (NALA)

Study Number: PUMA-NER-1301

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws, regulations and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

_____

Signature

_____ _____

Name Date

_____

Title

Declaration of Principal Investigator

Title: A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2-Directed Regimens in the Metastatic Setting (NALA)

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The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____

Signature

_____ _____

Name Date

_____ _____

Title Institution (block letters)

_____ _____

Address Phone number

17 APPENDICES

Appendix 1

Table A1. 1 Schedule of Procedures

Assessment Time Point									
Study Event	**Screening[a]**	**Baseline**	**Cycle 1 (21-Day Cycle)**			**Cycle 2+**	**Treatment Discontinuation**	**Safety Follow-up Contact**	**Long-Term Follow-up**
Study Days	**Within 21 Days Before Randomization**	**Within 72 Hours Before Randomization**	**Day 1**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 1 (±2 days)**	**0-3 Days After Last Dose**	**28 Days After Last Dose (+5 days)**	**Every 12 Weeks Post TD (±7 days)**
Procedures									
Informed Consent[b]	X								
Demographics	X								
Medical, Cancer and Medication History[c]	X								
Physical Examination[d]	X	X[e]				X	X		
Vital Signs, height and weight[f]	X	X[e]		X	X	X	X		
ECG[g]	X					X[g]	X[g]		
ECHO/MUGA[h]	X					X[h]	X		
ECOG Status	X	X[e]				X	X		
Heath Outcomes Assessments[i]		X[e]				X[i]	X		
Concomitant Therapy		Collected continuously throughout study period, including each visit						X	
Adverse Events[j]		Collected continuously throughout study period, including each visit						X	
Cancer Therapy[k]								X	X
HER2/ER/PR status (by central lab)[l]	X[l]								
Serum Pregnancy Test[m]	X								

Assessment Time Point									
Study Event	**Screening[a]**	**Baseline**	**Cycle 1 (21-Day Cycle)**			**Cycle 2+**	**Treatment Discontinuation**	**Safety Follow-up Contact**	**Long-Term Follow-up**
Study Days	**Within 21 Days Before Randomization**	**Within 72 Hours Before Randomization**	**Day 1**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 1 (±2 days)**	**0-3 Days After Last Dose**	**28 Days After Last Dose (+5 days)**	**Every 12 Weeks Post TD (±7 days)**
Laboratory									
Hematology Panel[n]	X	X[e]				X	X		
Serum Chemistry Panel[o]	X	X[e]				X	X		
Urine Dipstick[p]	X	X[e]							
Efficacy Assessments									
CT/MRI[a, i, q]	X					X[i]			
Survival[r]								X	X
Drug Administration (1st dose no later than 14 days after randomization)									
Neratinib (Arm A) or Lapatinib (Arm B)			Days 1 - 21 of each cycle						
Capecitabine			Days 1 - 14 of each cycle						
Antidiarrheal Treatment[s]			Prior to Neratinib administration						
Dosing Compliance				X	X	X	X		
PK Sampling at Select Study Centers									
PK Sampling[t]			X		X				

a. Screening activities are to be conducted within 21 days before randomization. Tumor scans (CT and MRI) and ECHO/MUGA must be performed within 28 days prior to randomization, and preferably no more than 28 days before initiation of treatment.
Randomization should occur after all baseline assessments have been completed and the site confirms that the patient still meets all eligibility requirements.

b. Informed consent must be obtained before any screening procedures begin.

c. Collect demographic information, relevant medical history, medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of screening, any medical conditions that require medication, and all prior cancer therapies. Identify the start of current medical conditions by at least the month/year; identify the start of significant preexisting conditions by at least the year.

d. Full physical exam at screening and brief physical exams at all subsequent time points to assess changes from the screening exam.

e. Baseline physical exam, vital signs, ECOG status, laboratory assessments, and health outcomes assessments must all be done within 72 hours prior to randomization. However, if screening laboratory assessments and ECOG status were performed within 72 hours before randomization and there were no clinically significant findings, these procedures do not need to be repeated.

f. Vital signs include pulse, blood pressure (after 5 min rest), and temperature (°C or °F; oral, core [rectal], axillary or tympanic); also measure height (screening only) and weight.

g. ECGs should be performed at Cycle 3/Day 1, Cycle 6/Day 1 and Day 1 of every 6th subsequent cycle during the active treatment phase. ECG should also be performed at Treatment Discontinuation if not done within the previous 12 weeks. Patients using drugs known to cause QT/QTc prolongation should be monitored closely with serial ECGs at the Investigator's discretion. Refer to Appendix 6 for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing Torsade de Pointes (TdP).

h. For LVEF during the active treatment phase, MUGA/ECHO should be repeated at Cycle 3/Day 1, Cycle 6/Day 1 and Day 1 of every 6th subsequent cycle. MUGA/ECHO should also be performed at Treatment Discontinuation if not done within the previous 12 weeks.

i. Timing for tumor assessments and health outcomes assessments (EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-5L) at the end of every 6 weeks (±3 days) is intended to reflect the end of every second cycle of study treatment. However, if cycles move off schedule for any reason, these assessments should remain every 6 weeks starting from Cycle 1/Day 1 during the active treatment phase. Tumor assessments will continue every 6 weeks until documented disease progression or death, regardless of whether the patient is continuing study treatment or has discontinued study treatment. The scans must be obtained and reviewed prior to start of the next cycle. For patients who show a CR on one scan and on a confirmatory scan obtained 6 weeks later, the frequency of subsequent scans may be reduced at the discretion of the investigator to no less than one scan every 12 weeks.

j. Serious adverse events (SAEs) must be reported starting at the time of signing informed consent. All AEs including SAEs must be reported from initiation of study treatment and must continue to be followed for 28 days after last administration of investigational product.

k. Cancer therapies evaluated at the safety follow-up contact and at the long-term follow-up contact include anti-cancer medications, cancer-related radiotherapy and cancer-related surgery/procedures since last contact.

l. Tumor testing for HER2 gene amplification or overexpression will be performed by a central laboratory using HercepTest™ and possibly FISH analysis using IQFISH pharmDx™. ER/PR status will be determined using pharmDx™ kit. Either primary breast cancer tissue (e.g., from prior surgical resection) or other breast cancer-containing tissue (e.g., from biopsy or excision of cancer-containing lymph node or metastatic lesion) is acceptable for central HER2 testing (see Section 8.2.1.1).

m. If a pregnancy test needs to be repeated during screening, a urine pregnancy test will suffice.

n. Hematology panel: differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils), hematocrit, hemoglobin (Hb), international normalized ratio (INR), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), red blood cell count (RBC), red blood cell distribution width (RDW), white blood cell count (WBC) with differential.

o. Serum chemistry includes at least the following: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorous, potassium, total protein, and sodium. Creatinine clearance will be calculated by the Cockroft-Gault Formula or Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 1999) within 14 days of enrollment.

p. Urinalysis by dipstick (blood, protein, glucose, and microscopic examination, if abnormal).

q. Post-treatment disease assessment by CT scan or MRI of the chest, abdomen and pelvis will be conducted every 6 weeks (±3 days). Tumor assessments will continue every 6 weeks until documented disease progression or death, regardless of whether the patient is continuing or has discontinued study treatment. Overall response will be scored by the Investigator according to RECIST v1.1 using the algorithms defined in Appendix 7. For patients who show a CR on one scan and on a confirmatory scan obtained 6 weeks later, the frequency of subsequent scans may be reduced at the discretion of the investigator to no less than one scan every 12 weeks.

r. Long-term follow-up for survival status will occur via telephone call if the site is unable to confirm via chart review.

s. Antidiarrheal treatment should be dispensed with the initial supply of neratinib.

t. At select study centers only: PK samples should be collected on Cycle 1, Day 1 and Day 15, at 6 hours post-dose (±20 minutes) and 8 hours post-dose (±60 minutes). Patients should be instructed to record the exact minute that the dose was taken on these days. PK samples will be taken from approximately 100 patients on the neratinib arm (Arm A).

Appendix 2

Investigational Product Dose Adjustment for Toxicity

1. DOSE ADJUSTMENT LEVELS

Recommended dose reductions for the -1 and -2 dose levels of **neratinib, lapatinib** and **capecitabine** are provided in Section 6.1.3.

2. TOXICITIES REQUIRING INVESTIGATIONAL PRODUCT DOSE ADJUSTMENTS

NERATINIB PLUS CAPECITABINE

General Toxicities

Guidelines for dose adjustments of **neratinib** and **capecitabine** for general toxicities due to combination of neratinib plus capecitabine are shown in Table A2. 1.

Table A2. 1 General Toxicities Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE v.4.0	Action
Grade 2 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume both drugs at the starting dose level.
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 3rd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 4th appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID).
• 2nd appearance	• Hold **neratinib** and **capecitabine** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).
• 3rd appearance	• Discontinue **neratinib** and **capecitabine** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** and **capecitabine** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** and **capecitabine** until resolved to Grade ≤1; then resume **neratinib** at 120 mg and **capecitabine** at 750 mg/m^2 (375 mg/m^2 BID).

Abbreviations: BID, twice daily; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Gastrointestinal Toxicity

Guidelines for adjusting doses of **neratinib** and **capecitabine** in the event of gastrointestinal toxicities are shown in Table A2. 2.

Table A2. 2 Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE v.4.0	Actions
Grade 1 Diarrhea: Increase of <4 stools per day over baseline; mild increase in output compared to baseline. OR **Grade 2 Diarrhea:** Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline. **Lasting ≤5 days** OR **Grade 3 Diarrhea:** Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care and activities of daily living. **Lasting ≤2 days**	• Adjust antidiarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 7.1.1). • Continue **neratinib** and **capecitabine** at full doses. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea (refer to Section 7.1.1). • Fluid intake of ~2 L/day should be maintained to avoid dehydration. • Once the event resolved to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.
Persisting and intolerable Grade 2 Diarrhea: lasting >5 days despite treatment with optimal medical therapy, or associated with fever, dehydration, or Grade 3-4 neutropenia. OR **Grade 3 Diarrhea:** lasting >2 days despite treatment with optimal medical therapy, or associated with fever, dehydration, or Grade 3-4 neutropenia. OR **Any Grade 4 diarrhea:** Life-threatening consequences: urgent intervention indicated.	• Adjust antidiarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to Section 7.1.1). • Hold **neratinib** and **capecitabine** until recovery to Grade ≤1 or baseline. • Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea. • Fluid intake of ~2 L/day should be maintained by IV, if needed. • If recovery occurs: o ≤1 week after withholding treatment, resume same doses of **neratinib** and **capecitabine**. o Within 1-3 weeks after withholding treatment, reduce **neratinib** dose to 160 mg and maintain the same dose of **capecitabine**. • If event occurs a second time and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to 160 mg (maintain the same dose of **capecitabine**). If **neratinib** dose has already been reduced, then reduce the dose of **capecitabine** to 1100 mg/m^2 (550 mg/m^2 BID)[a] (maintain the same dose of **neratinib**). • If subsequent events occur, reduce the dose of **neratinib** or **capecitabine** to the next lower dose level in an alternate fashion (i.e., reduce **capecitabine** to 750 mg/m^2 (375 mg/m^2 BID)[b] if **neratinib** was previously reduced, or reduce **neratinib** to 120 mg if **capecitabine** was previously reduced).

NCI CTCAE v.4.0	Actions
	• Once the event resolved to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Abbreviations: BID: twice daily; IV: intravenous; L: liter; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.
[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Pulmonary Toxicity

Guidelines for adjusting doses of **neratinib** in the event of pulmonary toxicity are shown in Table A2. 3. Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target HER1 ± HER2, including **lapatinib**, gefitinib and erlotinib. Rare cases of pneumonitis (0.6%) and lung infiltration (0.4%) have been reported in patients treated with **neratinib** monotherapy, and were considered drug-related. Patients receiving **neratinib** should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough and fever and treated appropriately.

Table A2. 3 Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE v.4.0	Actions
Grade 2 Pneumonitis/Interstitial Lung Disease: Symptomatic; medical intervention indicated; limiting instrumental activities of daily living.	• Hold **neratinib** until recovery to Grade ≤1 or baseline. • Reduce **neratinib** to 160 mg or discontinue **neratinib** per Investigator's best medical judgment.
Grade ≥3 Pneumonitis/Interstitial Lung Disease: Severe symptoms; limiting self-care activities of daily living; oxygen indicated.	• Discontinue **neratinib** permanently.

Abbreviations: NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Liver Toxicity

Guidelines for dose adjustment of **neratinib** and **capecitabine** in the event of liver toxicity are shown in Table A2. 4.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

Patients who experience Grade ≥3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for changes in liver function tests. Fractionated bilirubin and PT must also be collected during hepatotoxicity evaluation.

Table A2. 4 Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE v.4.0	Actions
Grade 3 ALT (>5-20 x ULN) or Grade 3 bilirubin (>3-10 x ULN)	• Hold **neratinib** and **capecitabine** until recovery to Grade ≤1 for patients with ALT Grade ≤1 at baseline OR Grade ≤2 for patients with Grade 2 ALT at baseline. • Evaluate alternative causes. • For patients with ALT Grade ≤1 at baseline: resume at a reduced doses of **neratinib** 160 mg and **capecitabine** at 1100 mg/m^2 (550 mg/m^2 BID)[a] if recovery to Grade ≤1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite the above-mentioned dose reduction, permanently discontinue **neratinib** and **capecitabine**. • For patients with Grade 2 ALT at baseline due to liver metastases: contact the Sponsor for guidance on appropriate dose adjustments.
Grade 4 ALT (>20 x ULN) or Grade 4 Bilirubin (>10 x ULN)	• Permanently discontinue **neratinib** and **capecitabine**. • Evaluate alternative causes.
ALT >3 x ULN and Total bilirubin >2 x ULN and Alkaline phospatase <2 x ULN (potential Hy's law indicators of drug-induced liver damage)	• Hold **neratinib** and **capecitabine**. The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and for oncology studies, the possibility of hepatic neoplasm (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, total bilirubin, direct bilirubin, PT and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, concomitant medications, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned above (i.e., ALT >3 x ULN associated with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN), with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's Law cases should be reported as SAEs. • Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product. • These events must be reported as SAEs.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; PT: prothrombin time; SAE: serious adverse event; ULN: upper limit of normal.
NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, PT must be measured, and liver imaging should be considered.
[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is rounded down to the nearest 500 mg or multiple of 150 mg for the BID dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Left Ventricular Ejection Fraction Toxicity

Guidelines for dose adjustments of **neratinib** in the event of abnormalities in LVEF are shown in Table A2. 5. LVEF assessments will be performed according to the Schedule of Procedures (Appendix 1). It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each time point for each patient.

Table A2. 5 Left Ventricular Ejection Fraction (LVEF) Results Requiring Dose Adjustment of Neratinib

Event on day of scheduled treatment	Actions
Asymptomatic absolute decline of LVEF ≥15% from baseline OR absolute decline of LVEF ≥10% and below the lower limit of normal of 50%	A) If LVEF is below 40%: Hold **neratinib** and seek cardiology input OR continue **neratinib** with great caution. Initiate monthly monitoring of LVEF • If while monitoring monthly, LVEF remains <40%: reconsider **neratinib** only if appropriate and after cardiology consult. • If while monitoring monthly, LVEF increases to ≥40%: continue **neratinib**, monitor LVEF every 12 weeks and consider cardiac support with input from cardiologist. B) If LVEF is between 40% to 50%: continue **neratinib** with caution and surveillance. Initiate monthly monitoring of LVEF • If while monitoring monthly, LVEF falls to <40%: Follow bullet point A instructions described above. • If while monitoring monthly, LVEF remains ≥40%: continue **neratinib**, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.
Symptomatic cardiac failure	• **Neratinib** should be discontinued.

Abbreviations: LVEF: left ventricular ejection fraction

If a patient has a second episode of asymptomatic decline in LVEF that meets either of the above criteria, permanently discontinue **neratinib**, repeat LVEF in 3-4 weeks and consider cardiology consult.

Note that, for AEs other than asymptomatic LVEF decline, if **neratinib** is held for >28 days, the patient should be withdrawn from the active treatment phase of the study (see Section 10.1). In case of asymptomatic LVEF decline, patients may resume **neratinib** within 1 week after LVEF recovery is documented as above, even if the timeframe exceeds 3 weeks. If a site does not provide normal ranges for ECHO or MUGA, a LLN of 50% should be used.

Hematologic Toxicity

Patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with **capecitabine**. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with **capecitabine** should be held.

Guidelines for dose adjustments of **capecitabine** for hematologic toxicity due to combination of neratinib plus capecitabine are shown in Table A2. 6.

Table A2. 6 Hematologic Abnormalities Requiring Dose Adjustment of Capecitabine (When Administered in Combination with Neratinib)

NCI CTCAE v. 4.0	Action
Grade 3 Neutrophil: <1000-500/mm^3; <1-0.5 × 10^9/L Platelet: <50,000-25,000/mm^3; <50-25× 10^9/L Hemoglobin decreased: <8 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• Neratinib should be continued at the same dose. • Hold capecitabine until event resolves or decreases to Grade 1 or Grade 2 • Reduce next capecitabine dose to 1100 mg/m^2 (550 mg/m^2 BID). • If the event recurs a 2nd time, hold capecitabine until event resolves or decreases to Grade 1 or Grade 2 • Reduce next capecitabine dose to 750 mg/m^2 (375 mg/m^2 BID) • If the event recurs/persists, discontinue capecitabine permanently.
Grade 4 Neutrophil: <500/mm^3; <0.5 × 10^9/L Platelet: <25,000/mm^3; <25 × 10^9/L Hemoglobin decreased: Life-threatening consequences; urgent intervention indicated	• Neratinib should be continued at the same dose. • Capecitabine should be discontinued permanently OR if the Investigator deems it to be in the patient's best interest to continue, hold capecitabine until resolved to Grade ≤1 • If the Investigator decides to resume capecitabine, reduce the dose to 750 mg/m^2 (375 mg/m^2 BID) • If the event recurs/persist, discontinue capecitabine permanently.

Abbreviations: BID: twice daily; L: liter; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Hand and Foot Syndrome

Guidelines for dose adjustments of **neratinib** and **capecitabine** for toxicity of Hand and Foot syndrome (Palmar-Plantar Erythrodysesthesia syndrome) due to combination of neratinib plus capecitabine are shown in Table A2. 7.

Table A2. 7 Hand-and-Foot Syndrome (Palmar-Plantar Erythrodysesthesia Syndrome) Requiring Dose Adjustment of Neratinib and Capecitabine

NCI CTCAE v.4.0	Action
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	• Continue **neratinib** and **capecitabine** at starting dose.
Grade 2: Skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain; limiting instrumental ADL. PI: painful erythema and swelling of the hands and/or feet and/or discomfort affecting ADL.	• Continue **neratinib** at starting dose level and hold **capecitabine** until recovery or to ≤grade 1, then resume at starting dose. • If the event recurs/persists, continue **neratinib** at starting dose level and reduce **capecitabine** dose to1100 mg/m^2 (550 mg/m^2 BID).
Grade 3: Severe skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain; limiting self-care ADL. PI: moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort limiting self-care ADL.	• Continue **neratinib** at starting dose level and hold **capecitabine** until recovery or to grade ≤1, then reduce dose to1100 mg/m^2 (550 mg/m^2 BID). • If the event recurs/persists, continue **neratinib** at starting dose level and reduce **capecitabine** dose to 750 mg/m^2 (375 mg/m^2 BID).

Abbreviations: ADL, activities of daily living; BID, twice daily; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

LAPATINIB PLUS CAPECITABINE

General Toxicities

Guidelines for dose adjustments of **lapatinib** and **capecitabine** for general toxicities due to combination of lapatinib plus capecitabine are shown in Table A2. 8.

Table A2. 8 General Toxicities Requiring Dose Adjustment of Lapatinib and Capecitabine

NCI CTCAE v.4.0	Action
Grade 2 adverse reaction	
• 1st appearance	• Hold **lapatinib** and **capecitabine** until event resolves to Grade ≤1; then resume **lapatinib** dose at 1250 mg and **capecitabine** at the starting dose level.
• 2nd appearance	• Hold **lapatinib** and **capecitabine** until event resolves to Grade ≤1; then resume **lapatinib** dose at 1000 mg and **capecitabine** dose at 1500 mg/m^2 (750 mg/m^2 BID).
• 3rd appearance	• Discontinue **lapatinib** permanently. • Hold **capecitabine** until event resolves to Grade ≤1; then resume **capecitabine** at 1000 mg/m^2 (500 mg/m^2 BID).
• 4th appearance	• Discontinue **capecitabine** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **lapatinib** and **capecitabine** until event resolves to Grade ≤1; then resume **lapatinib** dose at 1250 mg and **capecitabine** dose at 1500 mg/m^2 (750mg/m^2 BID).
• 2nd appearance	• Hold **lapatinib** and **capecitabine** until event resolves to Grade ≤1; then resume **lapatinib** dose at 1000 mg and **capecitabine** at 1000 mg/m^2 (500 mg/m^2 BID).
• 3rd appearance	• Discontinue **lapatinib** and **capecitabine** permanently.
Grade 4 adverse reaction	
1st appearance	• Discontinue **lapatinib** and **capecitabine** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **lapatinib** and **capecitabine** until resolved to Grade ≤1; then resume **lapatinib** at 1000 mg and **capecitabine** at 1000 mg/m^2 (500 mg/m^2 BID).

Abbreviations: BID, twice daily; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Gastrointestinal Toxicity

Guidelines for dose adjustments of **lapatinib** and **capecitabine** for gastrointestinal toxicity are shown in Table A2. 9.

Table A2. 9 Gastrointestinal Toxicities Requiring Dose Adjustment of Lapatinib and Capecitabine

NCI CTCAE v.4.0	Action
Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	• Continue **lapatinib** and **capecitabine** at starting dose. • Instruct patient to follow dietetic recommendations provided at the start of the study. Fluid intake of ~2L should be maintained to avoid dehydration.
Grade 2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline.	• Continue **lapatinib** and hold **capecitabine** until recovery to ≤ Grade 1 or baseline. Consider prophylactic antidiarrheal medications with next investigational product administration. • If recovery occurs in ≤1 week of treatment being held, resume **capecitabine** at starting dose. • If event persists/recurs, or if recovery occurs within 1-3 weeks of treatment being held, reduce dose of **lapatinib** to 1000 mg and **capecitabine** to 1500 mg/m^2 (750 mg/m^2 BID). • Following reoccurrence of Grade 2, adjust next dose of **capecitabine** to 1000 mg/m^2 (500 mg/m^2 BID).
Grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting ≥ NCI CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration) **or** **Grade 3:** Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline, limiting self-care ADL.	• Hold **lapatinib** and **capecitabine** until recovery to ≤Grade 1 or baseline. • May require administration of oral or IV fluids and electrolytes. Consider prophylactic antidiarrheal medications with next investigational product administration. • If recovery occurs in ≤1 week of treatment being held, resume **lapatinib** and **capecitabine** at starting dose. • If event persists/recurs, or if recovery occurs within 1-3 weeks of treatment being held, reduce **lapatinib** dose to 1000 mg and **capecitabine** dose to 1500 mg/m^2 (750 mg/m^2 BID).
Grade 4: Life-threatening consequences; urgent intervention indicated.	• Discontinue **lapatinib** permanently. • Hold **capecitabine** until recovery to ≤ Grade 1 or baseline. Consider prophylactic antidiarrheal medications with next investigational product administration. • If recovery occurs in ≤1 week of treatment being held, resume **capecitabine** at starting dose. • If event persists/recurs, or if recovery occurs within 1-3 weeks of treatment being held, reduce dose of **capecitabine** to 1500 mg/m^2 (750 mg/m^2 BID).

NCI CTCAE v.4.0	Action
	• Following reoccurrence of Grade 4, discontinue **capecitabine** permanently.

Abbreviations: ADL: activities of daily living; BID, twice daily; IV: intravenous; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Pulmonary Toxicity

Guidelines for adjusting doses of lapatinib in the event of pulmonary toxicity are shown in Table A2. 10**.**

Table A2. 10 Pulmonary Toxicities Requiring Dose Adjustment of Lapatinib

NCI CTCAE v.4.0	Action
Grade ≥3 Pneumonitis/Interstitial Lung Disease: Severe symptoms; limiting self-care ADL; oxygen indicated.	Discontinue **lapatinib** treatment permanently.

Abbreviations: ADL: activities of daily living; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Hepatic Toxicity

Guidelines for adjusting doses of **lapatinib** and **capecitabine** in the event of hepatic toxicities are shown in Table A2. 11.

Table A2. 11 Liver Function Test Abnormality Requiring Dose Adjustment of Lapatinib and Capecitabine

<table>
<tr><th colspan="2">NCI CTCAE v.4.0</th><th>Action</th></tr>
<tr><td colspan="2">ALT or AST Grade 3:
>5-20 x ULN;
>5 x ULN for >2 weeks.
or
ALT or AST Grade 4: >20 x ULN
AND
Total bilirubin > 2 x ULN</td><td>• Discontinue lapatinib permanently.</td></tr>
<tr><td colspan="2">Grade 3 hyperbilirubinemia
(>3-10 x ULN)</td><td>• Discontinue lapatinib permanently.
• Hold capecitabine until hyperbilirubinemia resolves or decreases to Grade 1 (ULN-1.5 x ULN) or Grade 2 (>1.5 x ULN).
• Reduce next capecitabine dose to 1500 mg/m^2 (750 mg/m^2 BID).</td></tr>
<tr><td colspan="2">Grade 4 hyperbilirubinemia
(>10 x ULN)</td><td>• Discontinue lapatinib and capecitabine permanently.
OR
• If the Investigator deems it to be in the patient's best interest to continue, hold capecitabine until event has resolved to Grade ≤ 1 (ULN-1.5 x ULN).
• If the Investigator decides to resume capecitabine, reduce capecitabine dose to 1000 mg/m^2 (500 mg/m^2 BID).</td></tr>
<tr><td colspan="3">LAPATINIB Dose Adjustment in Subjects with Severe Hepatic Impairment (Child-Pugh Class C)</td></tr>
<tr><td>Test</td><td>Result</td><td rowspan="6">• HER2+ MBC: Reduce lapatinib dose to 750 mg.
• HR+, HER2+ breast cancer: Reduce lapatinib dose to 1000 mg.</td></tr>
<tr><td>Total bilirubin</td><td>≥2 mg/dL;
≥34 µmol/L</td></tr>
<tr><td>Serum albumin</td><td>≤35 g/L</td></tr>
<tr><td>PT INR</td><td>≥1.7</td></tr>
<tr><td>Ascites</td><td>Mild to Severe</td></tr>
<tr><td>Hepatic encephalopathy</td><td>Grade 1-2 (or suppressed with medication)
Grade 3-4</td></tr>
</table>

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; ULN: upper limit of normal.

Left Ventricular Ejection Fraction Toxicity

Guidelines for adjusting dose adjustments of **lapatinib** when given in combination with **capecitabine** in the event of abnormalities in LVEF are shown in Table A2. 12.

Table A2. 12 Left Ventricular Ejection Fraction (LVEF) Results Requiring Dose Adjustment of Lapatinib when Administered in Combination with Capecitabine

NCI CTCAE v.4.0	Action
LV < ' L LN OR **Grade 2:** Resting EF 50-40%; 10-19% decrease from baseline OR **Grade 3:** Resting EF 39-20%; >20% decrease from baseline OR **Grade 4:** Resting EF <20%	• Hold **lapatinib**. • If, after a minimum of 2 weeks, the LVEF recovers to normal and the patient is asymptomatic, the patient may be restarted at a reduced dose of **lapatinib** 1000 mg with **capecitabine**.

Abbreviations: EF: ejection fraction; LLN: lower limit of normal; LVEF: left ventricular ejection fraction; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Hematologic Toxicity

Patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with **capecitabine**. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with **capecitabine** should be held.

Guidelines for dose adjustments of **capecitabine** for hematologic toxicity due to combination of capecitabine plus lapatinib are shown in Table A2. 13.

Table A2. 13 Hematologic Abnormalities Requiring Dose Adjustment of Capecitabine (When Administered in Combination with Lapatinib)

NCI CTCAE v.4.0	Action
Grade 3 **Neutrophil:** <1000-500/mm^3; <1-0.5 x 10^9/L **Platelet:** <50,000-25,000/mm^3; <50-25 x 10^9/L **Hemoglobin decreased:** <8 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• Hold **capecitabine** until event resolves or decreases to Grade 1 or Grade 2 • Reduce next **capecitabine** dose to 1500 mg/m^2 (750 mg/m^2 BID) • If the event recurs a 2nd time, hold capecitabine until event resolves or decreases to Grade 1 or Grade 2 • Reduce next **capecitabine** dose to 1000 mg/m^2 (500 mg/m^2 BID) • If the event recurs/persists, discontinue **capecitabine** permanently.
Grade 4 **Neutrophil:** <500/mm^3; <0.5 x 10^9/L **Platelet:** <25,000/mm^3; <25 x 10^9/L **Hemoglobin decreased:** Life-threatening consequences; urgent intervention indicated	• Discontinue permanently OR if the Investigator deems it to be in the patient's best interest to continue, hold **capecitabine** until resolved to Grade ≤1. • If the Investigator decides to resume **capecitabine**, reduce dose to 1000 mg/m^2 (500 mg/m^2 BID) • If the event recurs/persists, discontinue **capecitabine** permanently.

Abbreviations: BID: twice daily; L: liter; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Hand and Foot Syndrome

Guidelines for dose adjustments of **capecitabine** for toxicity of Hand and Foot Syndrome (Palmar-Plantar Erythrodysesthesia Syndrome) due to combination of capecitabine plus lapatinib are shown in Table A2. 14.

Table A2. 14 Hand-and-Foot Syndrome (Palmar-Plantar Erythrodysesthesia Syndrome) Requiring Dose Adjustment of Capecitabine (When Administered in Combination with Lapatinib)

NCI CTCAE v.4.0	Action
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain.	• Continue **capecitabine** at starting dose.
Grade 2: Skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain; **limiting instrumental ADL**. PI: painful erythema and swelling of the hands and/or feet and/or discomfort affecting ADL.	• Hold **capecitabine** until recovery or to Grade ≤1, then resume at starting dose. • If the event recurs/persists, reduce **capecitabine** dose to 1500 mg/m^2 (750 mg/m^2 BID).
Grade 3: Severe skin changes, e.g., peeling, blisters, edema, or hyperkeratosis, with pain; **limiting self-care ADL**. PI: moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort limiting self-care ADL	• Hold **capecitabine** until recovery or to Grade ≤1, then reduce to 1500 mg/m^2 (750 mg/m^2 BID). • If the event recurs/persists, reduce **capecitabine** dose to 1000 mg/m^2 (500 mg/m^2 BID).

Abbreviations: ADL: activities of daily living; BID: twice daily; NCI CTCAE v.4.0: National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; PI: Package Insert.

Appendix 3

Eastern Cooperative Oncology Group (ECOG) Performance Status

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix 4

Inhibitors and Inducers of the Cytochrome P450 Isoenzymes

CYP3A4 Inducers		
Carbamazepine	Phenobarbital	Rifapentine
Efavirenz	Phenylbutazone	St. John's Wort
Glucocorticoids:	Phenytoin	Sulfinpyrazone
Dexamethasone	Primidone	
Prednisone	Rifabutin	
Macrolide antibiotics	Rifampin	
CYP3A4 Inhibitors		
Amprenavir	Grapefruit juice	Propranolol
Anastrozole	Indinavir	Quinidine
Cimetidine	Itraconazole	Quinine
Clarithromycin	Ketoconazole	Ranitidine
Clotrimazole	Mibefradil	Ritonavir
Danazol	Miconazole	Saquinavir
Delavirdine	Mirtazapine (weak)	Sertraline
Diethyldithiocarbamate	Nefazodone	Sildenafil (weak)
Diltiazem	Nelfinavir	Troglitazone
Erythromycin	Nevirapine	Troleandomycin
Fluconazole	Norfloxacin	Zafirlukast
Fluoxetine	Norfluoxetine	
Fluvoxamine	Paroxetine	
CYP3A5-7 Inducers		
Phenobarbital	Primidone	Rifampin
Phenytoin		
CYP3A5-7 Inhibitors		
Clotrimazole	Metronidazole	Troleandomycin
Ketoconazole	Miconazole	
CYP2D6 Substrate		
Carvedilol	Hydrocodone	Propafenone
Chloroquine (possible)	Hydroxyamphetamine	Propoxyphene
Chlorpromazine	Labetalol	Propranolol (minor)
Citalopram	Maprotiline	Risperidone
Clozapine	Methamphetamine	Ritonavir
Codeine	Metoprolol	Ropivacaine
Cyclobenzaprine	Mexiletine (major)	Selegiline
Debrisoquin	Mirtazapine	Sertraline
Delavirdine	Morphine	Sparteine
Dexfenfluramine	Olanzapine	Tamoxifen
Dextromethorphan	Ondansetron	Thioridazine
Dolasetron	Oxaminiquine	Timolol
Donepezil	Oxycodone	Tolterodine (major)
Encainide	Paroxetine	Tramadol
Flecainide	Penbutolol	Trazodone
Fluoxetine	Pentazocine	Tricyclic antidepressants (Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Trimipramine)
Fluphenazine	Perphenazine	Venlafaxine
Halofantrine	Phenformin	Ziprasidone
Haloperidol	Primaquine (possible)	Zolpidem

Source: Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 2012.

Appendix 5

Substrates and Inhibitors of P-glycoprotein (P-gp)

P-glycoprotein Substrates		
Amiodarone (eg, Cordarone)	Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)
Chlorpromazine (eg, Thorazine)	Hydrocortisone (eg, Cortef)	Promethazine (eg, Phenergan)
Clarithromycin (eg, Biaxin)	Indinavir (Crixivan	Quinidine
Cyclosporine (eg, Neoral)	Itraconazole (eg, Sporanox)	Reserpine
Dactinomycin (Cosmegen)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Daunorubicin (eg, Cerubidine)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Dexamethasone (eg, Decadron)	Loperamide (eg, Imodium)	Sirolimus (Rapamune)
Digoxin (eg, Lanoxin)	Lovastatin (eg, Mevacor)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Mifepristone (Mifeprex)	Tamoxifen (eg, Nolvadex)
Doxorubicin (eg, Adriamycin)	Mitoxantrone (Novantrone)	Teniposide (Vumon)
Erythromycin (eg, Ery-Tab)	Nelfinavir (Viracept)	Testosterone Delatestryl)
Estradiol (eg, Estrace)	Nicardapine (eg, Cardene)	Trifluoperazine
Etoposide (eg, Vepesid)	Nifedipine (eg, Procardia)	Verapamil (eg, Calan)
Felodipine (Plendil)	Ondansetron (Zofran)	Vinblastine (eg, Velban)
Fexofenadine (Allegra)	Paclitaxel (eg, Taxol)	Vincristine (eg, Vincasar PFS)
P-glycoprotein Inhibitors		
Amiodarone (eg, Cordarone)	Indinavir (Crixivan)	Quinidine
Atorvastatin (Lipitor)	Itraconazole (eg, Sporanox)	Reserpine
Chlorpromazine (eg, Thorazine)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Clarithromycin (eg, Biaxin)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Cyclosporine (eg, Neoral)	Mifepristone (Mifeprex)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Nelfinavir (Viracept)	Tamoxifen (eg, Nolvadex)
Erythromycin (eg, Ery-Tab)	Nicardipine (eg, Cardene)	Testosterone (Delatestryl)
Felodipine (Plendil)	Nifedipine (eg, Procardia)	Trifluoperazine
Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)	Verapamil (eg, Calan
Hydrocortisone (eg, Cortef)	Propranolol (eg, Inderal)	

Source: Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 2012.

Appendix 6

Drugs Associated With Risk of QT/QTc Prolongation Leading to Torsade de Pointes

Drugs Reported to Prolong QT Interval		
Analgesics		
Celecoxib (Celebrex)	Methadone (e.g., Dolophine, Methadose)	
Anesthetic agents		
Enflurane (e.g., Ethrane)	Halothane	
Isoflurane (e.g., Forane)		
Antiarrhythmic agents		
Class IA	Class III	
Disopyramide (e.g., Norpace)*	Amiodarone (e.g., Cordarone)*[b]	
Procainamide (e.g., Procanbid)*	Bretylium*	
Quinidine*	Dofetilide (Tikosyn)*[b]	
Class IC	Ibutilide (Corvert)*[b]	
Flecainide (e.g., Tambocor)*[a]	Sotalol (e.g., Betapace)*[b]	
Propafenone (e.g., Rythmol)*[b]		
Anticonvulsants		
Felbamate (Felbatol)*	Fosphenytoin (Cerebyx)	
Antiemetics		
Dolasetron (Anzemet)[b]	Droperidol (e.g., Inapsine)*[b]	Ondansetron (Zofran)
Antihistamines		
Desloratadine (Clarinex)[b] (overdose)	Fexofenadine (Allegra)	
Diphenhydramine (e.g., Benadryl)	Hydroxyzine (Atarax)	
Anti-infectives		
Amantadine (e.g., Symmetrel)*	Macrolides and related antibiotics	
Antimalarials	Azithromycin (e.g., Zithromax)	
Mefloquine (e.g., Lariam)[b]	Clarithromycin (e.g., Biaxin)*[b]	
Quinine*	Erythromycin (e.g., Ery-Tab, EES)*[b]	
Antivirals	Telithromycin (Ketek)[b]	
Efavirenz (Sustiva)*	Troleandomycin	
Azole antifungal agents	Pentamidine (e.g., Pentam 300, Nebupent)*	
Fluconazole (e.g., Diflucan)*[b]	Quinolones	
Itraconazole (e.g., Sporanox)	Gatifloxacin (e.g., Tequin)*[b]	
Ketoconazole (e.g., Nizoral)	Levofloxacin (e.g., Levaquin)*[a, b]	
Voriconazole (Vfend)[b]	Moxifloxacin (e.g., Avelox)[b]	
Chloroquine (e.g., Aralen)*	Ofloxacin (e.g., Floxin)*[b]	
Clindamycin (e.g., Cleocin)	Sparfloxacin (Zagam)[b]	
Foscarnet (Foscavir)	Trimethoprim/sulfamethoxazole (e.g., Bactrim)*	
Antineoplastics		
Arsenic trioxide (Trixenox)*[b]	Doxorubicin (e.g., Adriamycin)	Tamoxifen (e.g., Nolvadex)
Bronchodilators		
Albuterol (e.g., Proventil)[b]	Salmeterol (Serevent)[b]	
Formoterol (Foradil)[b]	Terbutaline (e.g., Brethine)[b]	
Isoproterenol (e.g., Isuprel)		
Calcium channel blockers		
Isradipine (DynaCirc)	Nicardipine (e.g., Cardene)	

Drugs Reported to Prolong QT Interval		
Contrast media		
Ionic contrast media*	Non-ionic contrast media: Iohexol (Omnipaque)	
Corticosteroids		
Prednisolone (e.g., Prelone)	Prednisone (e.g., Deltasone)*	
Diuretics		
Furosemide (e.g., Lasix)	Indapamide (e.g., Lozol)	
Gastrointestinal agents		
Cisapride (Propulsid)*[b, c]	Famotidine (e.g., Pepcid)*	
Immunosuppressants		
Tacrolimus (Protopic)*[b] (postmarketing)		
Miscellaneous		
Levomethadyl	Papaverine (e.g., Pavaden three times daily [TID])*	
Moexipril/Hydrochlorothiazide (Uniretic)	Probucol (Lorelco)*[c]	
Octreotide (Sandostatin)[b]	Vasopressin (e.g., Pitressin)*	
Oxytocin (e.g., Pitocin; intravenous bolus)		
Psychotropics		
Droperidol (e.g., Inapsine)*	Primozide (Orap)*[b, d]	Trazodone (e.g., Desyrel)
Haloperidol (e.g., Haldol)*	Quetiapine (Seroquel)[b]	Tricyclic antidepressants
Lithium (e.g., Eskalith)*	Risperidone (Risperdal)[b] (overdose)	Amitriptyline*
Maprotiline*	Serotonin Reuptake Inhibitors (SRIs)	Clomipramine (e.g., Anafranil)
Phenothiazines	Citalopram (e.g., Celexa)*	Desipramine (e.g., Norpramin)*
Chrlorpromazine (e.g., Thorazine)*	Fluoxetine (e.g., Prozac)*[a]	Doxepin (e.g., Sinequan)*
Fluphenazine (e.g., Prolixin)*	Paroxetine (e.g., Paxil)*	Imipramine (e.g., Tofranil)*
Perphenazine	Sertraline (Zoloft)*[a, b] (postmarketing)	Nortriptyline (e.g., Pamelor)
Thioridazine (Mellaril)*[b]	Venlafaxine (Effexor)[b] (postmarketing)	
Trifluopherazine		
Serotonin 5-HT[1] agonists		
Naratriptan (Amerge)	Sumatriptan (Imitrex)[b]	Zolmitriptan (Zomig)[b]
Skeletal muscle relaxants		
Tizanidine (e.g., Zanaflex)[b] (animals)		

* Drugs for which Torsades de Pointes has also been reported.
[a] Association unclear
[b] QT, QTc and/or Torsades de Pointes association listed in FDA approved product labeling
Source:
Tatro, DS. Drug-induced Prolongation of the QT Interval and Torsades de Pointes. Drug Interaction Facts. The Authority on Drug Interactions. Wolters Kluwer Health 2012.

Appendix 7

RECIST v1.1 Criteria (Eisenhauer et al., 2009)

Patient Eligibility

Only patients with measurable disease at baseline should be included in this study. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability provides neither additional meaning nor accuracy and will not be used.

Measurable Disease

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Nonmeasurable Disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Target and/or non-target lesions should be selected from organs/sites that have not received local/focal therapy

(e.g., radiation therapy or radiofrequency ablation), unless disease progression has subsequently been radiologically confirmed after focal/local therapy. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations must be performed within 28 days prior to randomization, and preferably no more than 28 days before the initiation of treatment.

Method of assessment

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 should

always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup

has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

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

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

Progressive Disease (PD): At least a 20% increase in the sum of 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 progression).

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.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions.

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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).

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): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR: complete response; NE: not evaluated; PD: progressive disease; PR: partial response; SD: stable disease.

Note: Patients with a global deterioration of health status requiring discontinuation of investigational product without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of investigational product. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the CR status.

Confirmatory Measurement/Duration of Response

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular

in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). 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 (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD. Note: The DOR and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 8

Health Outcomes Assessment: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9

Health Outcomes Assessment: EORTC QLQ-BR23

ENGLISH

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 10

Health Outcomes Assessment: EQ-5D-5L

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

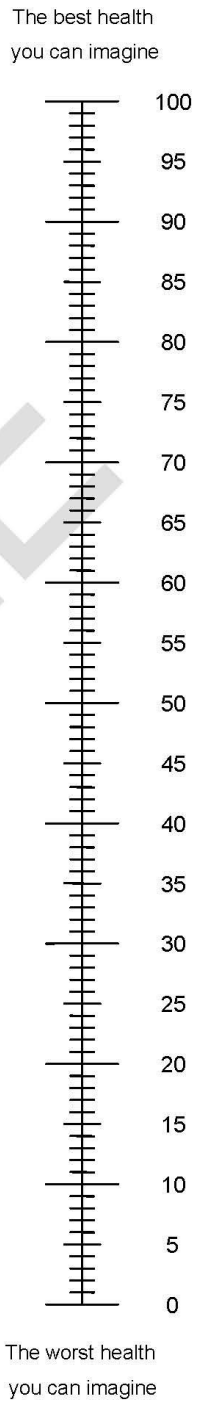
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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