NOVARTIS

Clinical Development

GW572016

Protocol EGF117165 / NCT02213042

An Open-Label, Phase II, Study to Evaluate Biomarkers Associated with Response to Subsequent Therapies in Subjects with HER2-Positive Metastatic Breast Cancer Receiving Treatment with Trastuzumab in Combination with Lapatinib or Chemotherapy

Authors	[redacted]
Document type	Amended Protocol Version (Clean)
EUDRACT number	2014-001220-30
Version number	03
Development phase	Phase II
Document status	Final
Release date	15-May-2017
Novartis internal reference number	CLAP016A2206

Amendment 3

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GW572016, the purpose of this protocol Amendment 3 is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of May 2017:

42 patients have received study treatment in five countries;

34 patients have completed or discontinued study treatment.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Description: This is a multicenter, open-label, Phase II study in subjects with HER2-positive metastatic breast cancer who received at least 2 prior lines of anti-HER2-targeted therapies of which at least one included a trastuzumab-containing regimen. Eligible subjects will have confirmed HER2-positive and hormonal status from a biopsy taken at screening (pre-treatment biopsy). Subjects will have consented to a subsequent biopsy at disease progression. Subjects will be assigned to one of two cohorts based on the molecular subtype of the pre-treatment biopsy by Prosigna. Eligible subjects with a HER2-enriched molecular subtype will be randomized in a 1:1 ratio to 1 of 2 treatment arms: trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily) or trastuzumab in combination with chemotherapy of the investigator's choice (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg q3weekly infusions and chemotherapy as decided by investigator). Eligible subjects with breast cancer classified as a molecular subtype complementary to the HER2-enriched referred to as Non-HER2-enriched (i.e., luminal A, luminal B or basal-like) will be enrolled into an additional arm treated with trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily). Subjects with hormone receptor positive breast cancer assigned to receive treatment with lapatinib and trastuzumab will be required to receive concomitant endocrine therapy with an aromatase inhibitor of the investigator's choice. Subjects with hormone receptor-positive disease assigned to the treatment arm of trastuzumab in combination with chemotherapy may receive concomitant endocrine therapy with an aromatase inhibitor, of the investigator's choice and at the discretion of the investigator. All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal or any other reasons mentioned in section 4.2.1. The primary endpoint is to evaluate the changes in the expression of biomarkers associated with immunomodulation between the progression biopsy and the pre-treatment biopsy within each arm. Secondary efficacy endpoints include overall response rate; clinical benefit rate; and progression-free survival (PFS) on treatment; as well as safety/tolerability. Due to difficulty in enrolling subjects, enrollment was halted and the study will be terminated early. No formal comparisons between treatment arms will be undertaken.

Subject: lapatinib, HER2-overexpressing metastatic breast cancer, trastuzumab, ErbB2, HER2, biomarker, PAM50, HER2-enriched, Prosigna

Revision Chronology:

2013N170247_0	No publishing date	Amendment No. 0 (original version): This version was never dispatched to the countries.
2013N170247_01	26-MAR-2014	Amendment No. 01: Global amendment: This version was amended to remove the third biopsy (based on the feedback from the countries). This version was the first one dispatched to the countries.
2013N170247_02	23-MAR-2017	Amendment No. 02: Global amendment: Study EGF117165 is a post-approval commitment required by the CHMP to evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy. Recruitment of patients into study EGF117165 has been difficult. Efforts to boost recruitment were undertaken but the prospect to significantly improve recruitment is poor, thus preventing Novartis from meeting the agreed timelines for completion. In addition, the results of this trial will likely become obsolete by the time of delayed completion. Therefore, Novartis proposes to terminate the study and to conduct a final analysis of the enrolled patients. In this context, the updates to the protocol are as follows: The Primary Objective was updated to remove the evaluation of changes in the expression of biomarkers associated with HER family, apoptosis, and ABC transporters. The Primary Objective now evaluates the changes in the expression of

biomarkers associated with immunomodulation.

The Secondary Objectives were updated to remove OS and PFS on first next line and subsequent lines of anti-cancer therapies. The Patient Reported Outcomes (PRO) and Health-Related Quality of Life (HRQOL) were also removed.

Section 4.2.3 Subject Completion: Follow-up time was re-defined as follows: A subject will be considered to have completed the study if the subject presents with disease progression, starts a new anti-cancer therapy, dies or withdraws from the study, or the study ends, whichever comes first. In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of

		study, whichever comes first.
2013N170247_03	15-May-2017	Amendment No. 03: Global amendment: Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Make administrative changes to align with Novartis processes and procedures.

Sponsor Signatory:	**Signature:**	**Date:**
Dr. [redacted]	_____	_____

SPONSOR INFORMATION PAGE

Clinical Study Identifier: EGF117165

Sponsor Contact Information

Novartis Pharma Services AG

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Serious Adverse Events (SAE) Contact Information:

Please refer to the study procedures manual.

For study conduct questions not related to patient safety, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available, please contact the Medical Lead.

[redacted]Contact Information:

[redacted] MD, PhD
[redacted]
Novartis Pharma AG
Postfach CH-4002 Basel
Switzerland
Telephone:[redacted]
Email: [redacted]

Regulatory Agency Identifying Number(s):

Eudra CT number: 2014-001220-30

IND Number: 61362

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

ABC	Adenosine triphosphate binding cassette
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AI	Aromatase inhibitor
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AV	Atrioventricular
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma-extra large
Bcl2L11	Bcl-2-like protein 11
β-HCG	beta human chorionic gonadotropin
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
BSA	Body surface area
BTC	β-cellulin
CBR	Clinical benefit rate
cfDNA	Circulating free DNA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EP	Evaluable Population
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDR	False discovery rate
FISH	Fluorescence in situ hybridization
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	Follicle stimulating hormone

g/dL	Grams/deciLiter
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBEGF	Heparin-binding EGF-like growth factor
HER	Human epidermal growth factor receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology System
ITT	Intent to Treat
IV	Intravenous(ly)
kg	Kilogram
L	Liter
LFT	Liver function test
LLN	Lower limit of normal
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
m^2	Meter squared
MAPK	Mitogen-activated protein kinase
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MSDS	Material Safety Data Sheet
MUGA	Multigated acquisition
MW	Molecular weight
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
OR	Odds ratio
ORR	Overall response rate
OTR	Optimally tolerated regimen
PAM	Prediction Analysis of Microarray
PAM50	Prediction Analysis of Microarray 50
PBMC	Peripheral blood mononuclear cells
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death 1
PDL-1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
PgR	Progesterone receptor
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PO	*Per os* (orally)

PR	Partial response
q3weekly	Every 3 weeks
QoL	Quality of life
QTcB	QT interval corrected for heart rate (Bazett's formula)
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SISH	Silver in situ hybridization
SPM	Study Procedures Manual
$t_{½}$	Half life
TDM-1	Trastuzumab emtansine
TGFα	Transforming growth factor α
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TTP	Time to progression
ULN	Upper limit of normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
TYKERB/ TYVERB

Trademarks not owned by the GlaxoSmithKline group of companies
Abraxane
Arimidex
Aromazine
Femara
Gemzar
Herceptin
InForm
Navelbine
Prosigna
Taxol
Taxotere
Xeloda

PROTOCOL SUMMARY

Rationale

Overexpression of human epidermal growth factor receptor 2 (HER2), the protein product of the *ERBB2* gene, occurs in approximately 20 percent of human breast cancers. Compared to other types of breast cancer, these cancers are associated with a greater risk for disease progression and death [Slamon, 1987; Meric, 2002] as well as resistance to chemotherapeutic and hormonal agents, and poorer prognosis [Slamon, 2001; Nicholson, 1999].

Trastuzumab has been extensively evaluated and represents a clinical breakthrough in treating patients with HER2-positive breast cancer. Trastuzumab in combination with chemotherapy is indicated as first-line treatment of patients with HER2-positive metastatic breast cancer. The combination regimen demonstrated a superior clinical benefit as compared to that observed with chemotherapy alone. In addition, trastuzumab has been shown to be effective in prolonging survival in women with ErbB2 amplified breast cancer when used in the adjuvant setting [Piccart-Gebhart, 2005; Perez, 2005; Romond, 2005; Joensuu, 2006; Smith, 2007; Slamon, 2011].

Progression on a trastuzumab-containing regimen eventually occurs in the metastatic setting. Limited data are available on the efficacy of continuation of trastuzumab in combination with chemotherapy compared to chemotherapy alone after progression on a trastuzumab containing regimen.

Subjects with HER2-positive metastatic breast cancer (MBC) randomized to capecitabine monotherapy or the continuation of trastuzumab in addition to capecitabine had an increased median time to progression from 5.6 months to 8.2 months (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.48 to 0.97) [von Minckwitz, 2009]. As such, common clinical practice incorporates the continued use of trastuzumab, usually in combination with chemotherapy, following progression of disease on a prior trastuzumab-containing regimen [Wong, 2011]. Declining clinical activity, however, is to be expected with each subsequent regimen with continued use of trastuzumab past progression [Pegram, 2012].

Trastuzumab conjugated to the cytotoxic microtubule inhibitor mertansine, trastuzumab emtansine (T-DM1) has been studied in subjects that have progressed on at least one prior trastuzumab-containing regimen. As the second line treatment of HER2-positive MBC, T-DM1 improved progression free survival (PFS) (HR = 0.65; 95% CI 0.55 to 0.77; $p<0.00$) as well as overall survival (OS)(HR = 0.68; 95% CI 0.55 to 0.85; $p<0.001$) compared with lapatinib in combination with capecitabine [Verma, 2012]. Compared to treatment of physician's choice, T-DM1 also improved PFS (HR = 0.528, 95% CI, 0.422, 0.661, $p<0.0001$) [Wildiers, 2013].

Lapatinib is a reversible, orally bioavailable, small molecule tyrosine kinase quinazoline inhibitor that potently inhibits both Epidermal Growth Factor Receptors (EGFR) and HER2. Lapatinib monotherapy demonstrated modest activity in MBC previously treated with trastuzumab [Blackwell, 2009]. Lapatinib is approved in combination with

capecitabine or trastuzumab in patients with HER2-overexpressing MBC and who have progressed on prior trastuzumab. Lapatinib is also indicated in combination with an aromatase inhibitor for the treatment of patients with hormone sensitive metastatic disease, not currently intended for chemotherapy [Lapatinib Summary of Product Characteristics, 2015].

Dual blockade: Lapatinib in combination with trastuzumab

Resistance to trastuzumab is considered to be a key factor in disease progression and is observed in the majority of patients with disease that initially responded to treatment.

There is a scientific rationale for combining two HER2-targeted agents with non-overlapping mechanisms of resistance and complementary mechanisms of action. Each drug targets a distinct functional domain of the HER2 receptor: trastuzumab, an IgG1 monoclonal antibody, binds to domain IV of the extracellular region whereas lapatinib, a tyrosine kinase inhibitor (TKI), binds to the adenosine triphosphate (ATP) site in the intracellular kinase domain. Preclinical evidence demonstrates that lapatinib and trastuzumab are synergistic in HER2-positive breast cell lines that are sensitive to trastuzumab as well as some that have acquired resistance to trastuzumab [Konecny, 2006]. In addition, it was shown that lapatinib is active in some cell lines that are resistant to trastuzumab. As such, the combination of trastuzumab and lapatinib (Dual blockade) is promising as the combination more completely inhibits HER2 signalling.

In the neoadjuvant setting, Dual blockade has shown a greater rate of pathological complete response (pCR) in combination with chemotherapy or without chemotherapy compared with trastuzumab or lapatinib alone.

In the metastatic setting, the combination of Dual blockade was compared with single HER2 inhibition with lapatinib monotherapy in subjects with HER2-positive tumors previously treated with trastuzumab in study EGF104900. The majority of subjects (81%) had 2 or more prior trastuzumab-containing regimens in the metastatic setting and had documented progression (by Response Evaluation Criteria in Solid Tumors [RECIST]) on a preceding trastuzumab-based therapy.

The primary endpoint of EGF104900 was PFS. The median PFS was longer in the Dual blockade arm (12.0 weeks) than in the lapatinib monotherapy arm (8.1 weeks) in the intent to treat (ITT) population with Strata (N=291). The hazard ratio (HR=0.73; 95% CI: 0.57 to 0.93; p=0.008) translates to a 27% reduction in risk of disease progression or death for subjects receiving Dual blockade therapy [Blackwell, 2010].

In a pre-planned analysis of OS when a total of 75% of the subjects had died, subjects in the Dual blockade arm had a longer median OS of 14.0 months compared with 9.5 months in the lapatinib monotherapy arm. The HR (HR=0.74; 95% CI: 0.57 to 0.97; stratified log rank p=0.026) translates to a 26% reduction in risk of death for subjects receiving Dual blockade therapy [Blackwell, 2012].

Subgroup analysis results based on the stratification factor of hormone receptor status showed that the efficacy of the Dual blockade in terms of OS was increased in subjects

with hormone receptor-negative tumors compared to those with hormone receptor-positive tumors, although the hazard ratios for PFS were similar (0.73).

Based on the final results of EGF104900, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has granted positive opinion for the regulatory approval for lapatinib, in combination with trastuzumab in HER2 positive metastatic breast cancer. As such, lapatinib plus trastuzumab is indicated for the treatment of patients with hormone receptor-negative metastatic breast cancer whose tumors overexpress HER2/neu (ErbB2) and who have progressed on prior trastuzumab therapy(s) in combination with chemotherapy in the metastatic setting.

The PFS/OS pattern observed in EGF104900, whereby a statistically significant but modest PFS gain associated with a larger and clinically meaningful OS benefit for Dual blockade, was also seen in another combination of two anti-HER2 agents. In the CLEOPATRA study [Baselga, 2012b; Swain, 2013], the median PFS was 12.4 months in subjects who received trastuzumab and docetaxel and 18.5 months in subjects who received pertuzumab with trastuzumab and docetaxel (HR: 0.65; 95% CI: 0.54 to 0.78; $p<0.001$). This represents a median improvement in PFS of 6.1 months. In an update of OS data [Swain, 2013], the median OS in subjects who received trastuzumab and docetaxel was 37.6 months and the median OS in subjects who received pertuzumab with trastuzumab and docetaxel had not been reached.

This unusual PFS/OS pattern has been observed in two phase III trials of two different combinations of anti-HER 2 agents. A potential mechanistic hypothesis to explain the unusual PFS/OS pattern is that Dual blockade may exert a “post-treatment effect” on subsequent therapies by modulating sensitivity to subsequent chemotherapy(ies) regimens.

Protocol EGF117165 is a phase II study evaluating whether treatment with Dual blockade promotes changes of biomarkers associated with immunomodulation.

Primary Objective:

- To evaluate changes in the expression of biomarkers associated with immunomodulation.

Secondary Objectives:

- To describe overall response rate (ORR), clinical benefit rate (CBR), and PFS on study treatment in subjects treated with trastuzumab in combination with lapatinib or chemotherapy.
- To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy.

[redacted]

[redacted]

Study Design

This is a multicenter, open-label, 3 arm, parallel group, Phase II study in subjects with HER2-positive metastatic breast cancer (MBC) who received prior treatment for metastatic disease including a trastuzumab-containing regimen. Subjects will have received treatment with at least 2 prior lines of treatment for MBC. Subjects will be required to have documented progression on their prior regimen for the treatment of MBC, which must have included trastuzumab and chemotherapy. During screening, all subjects will have a biopsy of their metastatic disease (pre-treatment biopsy). The central laboratory will perform testing on this biopsy to determine HER2 and hormone receptor status. The intrinsic molecular subtype also will be determined centrally from this pre-treatment biopsy. Based on molecular subtype classification, subjects will be eligible for one of 2 cohorts: randomized HER2-enriched cohort or non-randomized Non-HER2-enriched cohort. Subjects with a HER2-enriched molecular subtype will be randomized to treatment with trastuzumab in combination with lapatinib or trastuzumab in combination with chemotherapy of the investigator's choice. Subjects in the Non-HER2-enriched cohort will be assigned to treatment with trastuzumab in combination with lapatinib.

Subjects enrolled to trastuzumab in combination with lapatinib will receive a trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg PO of lapatinib once daily. Subjects enrolled to trastuzumab in combination with chemotherapy of the investigator's choice will receive a trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg q3weekly infusions and chemotherapy as decided by investigator. Subjects with hormone receptor-positive tumors from the baseline biopsy will be required to have a concomitant aromatase inhibitor with trastuzumab in combination with lapatinib however, for those subjects randomized to trastuzumab in combination with chemotherapy; a concomitant aromatase inhibitor is at the discretion of the investigator. In all treatment arms, weekly trastuzumab (loading dose of 4mg/kg followed by week infusions of 2mg/kg) can be administered rather than every 3 weeks if preferred.

At disease progression a biopsy should be taken from the same site as the pre-treatment biopsy. The comparison of gene and/or protein expression changes in these paired biopsies will be the basis for the primary objective.

All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal or any other reasons mentioned in section 4.2.1.

Study Assessments

The primary endpoint is to analyze the changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated with immunomodulation. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately.

Biopsies will be taken at screening (pre-treatment biopsy) and at the time of disease progression (progression biopsy). Disease assessments will be performed every 9 weeks until 54 weeks then every 24 weeks thereafter. [redacted]

Safety assessments including physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs and weight, adverse event (AE) monitoring, and laboratory tests (complete blood count, blood chemistry including liver function test) will be done at screening and then every 3 weeks for the duration of study treatment. Additional safety assessments, such as cardiac monitoring, are required for all subjects every 12 weeks until withdrawal from the study treatment.

1. INTRODUCTION

1.1. Background

1.1.1. Breast Cancer

Breast cancer is globally one of the most prevalent cancers, as improvements in early diagnosis and current advancements in treatment modalities have increased the survival rates for these patients. In the United States, there were approximately 2.6 million patients with breast cancer in 2007 [Howlader, 2011]. In Europe, data from 38 population-based cancer registries from 17 European countries (approximately 3 million patients diagnosed during 1970-1992) demonstrated that breast cancer accounted for 34% of all prevalent cancers in women [Micheli, 2002]. Population-based studies have suggested that with the introduction of novel therapeutic agents, women are living longer after a diagnosis of advanced cancer [Chia, 2007]. Despite improvements in early diagnosis and treatments, almost all patients with metastatic disease, and up to 40% of patients receiving adjuvant hormonal therapy, eventually relapse and ultimately die from their disease [Ring, 2003].

1.1.2. Role of HER2 Overexpression in Breast Cancer

Approximately 20% of human breast cancers exhibit gene amplification and/or overexpression of the Human epidermal growth factor receptor 2(HER2) receptor [Slamon, 1987; Slamon, 1989]. Due to the constant open conformation of extracellular domain II and high concentrations of the HER2 receptor on the cell surface, HER2 receptors homo-dimerize and ligand independent activation of the HER2 intraocular tyrosine kinase domain occurs [Garrett, 2003]. Activation of the HER2 and downstream pathways promotes cellular growth and survival through a variety of partially overlapping mechanisms.

Patients with HER2-overexpressing breast cancers have particularly aggressive disease that is associated with a greater risk for disease progression and death [Meric, 2002; Sauter, 2009]. HER2 receptor overexpression is associated with poorly differentiated, high-grade tumors, lymph node involvement, increased cellular proliferation, and a relative resistance to certain types of chemotherapy as well as an increased proclivity for central nervous system (CNS) metastases [Burstein 2005, Kallioniemi 1991,Gabos 2006].

Role of Trastuzumab in the Treatment of Breast Cancer

1.1.2.1. Preclinical Evidence for Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody which binds to the juxtamembrane extracellular subdomain IV of the HER2 receptor. Although the mechanisms by which trastuzumab inhibits HER2-overexpressing tumors are incompletely understood, several possible mechanisms have been observed in experimental preclinical *in vitro* and *in vivo* models, including internalization and degradation of HER2, inhibition of the HER2 ectodomain cleavage, modulation of the p27-Cdk2 complex formation, and induction of immune-mediated responses via the antibody-dependent cellular cytotoxicity (ADCC) function, a mechanism not

demonstrated by tyrosine kinase inhibitors [Campone, 2011]. Structural studies using recombinant HER2 receptor ectodomains, as well as in vitro experiments with HER2 monoclonal antibodies that recognize different receptor epitopes, indicate that trastuzumab binds in a region not involved in receptor dimerization [Cho, 2003; Agus, 2002]. Diminished receptor signalling may result from trastuzumab-mediated internalization and degradation of the HER2 receptor [Baselga, 2001; Sliwkowski, 1999]; although some researchers have demonstrated that receptor levels are unchanged in response to trastuzumab treatment [Austin, 2004].

1.1.2.2. Trastuzumab as First-Line Therapy for Metastatic Breast Cancer

Trastuzumab has been extensively clinically evaluated and has represented a clinical breakthrough in treating patients with HER2-positive breast cancer. As a single agent, trastuzumab has demonstrated activity in advanced and metastatic breast cancer. In patients who were previously treated with 1 to 2 lines of chemotherapy, response rates have ranged from 15% to 20% [Cobleigh, 1999]. In the first-line setting for metastatic breast cancer (MBC), a 26% overall response rate (ORR) (95% confidence interval [CI], 18.2 to 34.4) and median time to disease progression of 3.5 to 3.8 months were observed for weekly trastuzumab monotherapy [Vogel, 2002].

The above studies with trastuzumab monotherapy gave way to studies that combined chemotherapy with trastuzumab. Trastuzumab in combination with chemotherapy showed activity as first-line treatment of subjects with HER2-positive MBC. In combination with either an anthracycline or taxane as first-line treatment in MBC, the addition of trastuzumab increased the ORR, which ranged from 38% to 50%, with the highest difference observed in combination with paclitaxel versus paclitaxel alone. The survival advantage was greatest in the anthracycline and cyclophosphamide plus trastuzumab arm (median 26.8 months) versus anthracycline and cyclophosphamide only (21.4 months). A survival benefit also was seen in the paclitaxel plus trastuzumab arm (median 22.1 months) compared with paclitaxel alone (18.4 months), although this was not statistically significant [Slamon 2001]. More recently, trastuzumab in combination with pertuzumab and docetaxel for the treatment of first-line MBC extended progression free survival (PFS) from 12.4 months to 18.5 months (hazard ratio [HR] = 0.62; 95% CI 0.51 to 0.95; $p<0.001$) and trended toward improvement of overall survival (OS) [Baselga 2012b].

1.1.2.3. Continuation of Trastuzumab Post Progression of Disease

While the definition of trastuzumab-refractory and/or -resistant disease has not been clearly characterized [Wong, 2011], clinical practice has evolved to continue the use of sequential lines of trastuzumab-based therapies despite the lack of robust evidence from clinical studies to support this practice [Beslija, 2007]. As such, this approach has been acknowledged by national treatment guidelines [NCCN, 2010; Cardoso, 2012]. Several clinical questions, however, remain unanswered about the optimal use of trastuzumab in MBC following progression of disease. For example, after progression on trastuzumab and chemotherapy in the first-line setting in the study of Slamon and colleagues [Slamon, 2001], a subset of subjects continued with trastuzumab monotherapy. The ORR in these

subjects was 9%, substantially lower than the aforementioned 38% to 50% for first-line treatment [Tripathy, 2004].

When administered as an antibody-drug conjugate combining trastuzumab with the cytotoxic activity of the microtubule inhibitor DM1 (a derivative of maytansine), trastuzumab emtansine (T-DM1) as second-line treatment for MBC improved both PFS (9.6 versus 6.4 months; HR = 0.65; 95% CI 0.55 to 0.77; p<0.001) as well as OS (30.9 versus 25.1 months; HR = 0.68; 95% CI 0.55 to 0.85; p<0.001) compared with lapatinib in combination with capecitabine [Verma, 2012]. In subjects that received a median of 4 prior regimens for MBC, T-DM1 demonstrated a median PFS of 6.2 months compared to 3.3 months for treatment of physician's choice (HR = 0.528, 95% CI, 0.422, 0.661, p<0.0001) [Wildiers, 2013]. Treatment of physician's choice consisted mainly of trastuzumab-containing regimens (80.4% of the subjects had a trastuzumab containing regimen).

The safety and efficacy of trastuzumab also has been investigated with additional chemotherapy combinations in several smaller prospective, nonrandomized clinical trials and has been successfully combined with various cytotoxic therapies including vinorelbine, gemcitabine, and capecitabine, as well as nab-paclitaxel, paclitaxel, and docetaxel, with response rates ranging from 8% to 67% and median time to progression (TTP) of 3.5 to 9.5 months in the second-line and beyond MBC setting [Pegram, 2012].

Despite this treatment paradigm, evidence suggests that with each successive trastuzumab regimen in the metastatic setting, the clinical efficacy declines. As noted above, trastuzumab in combination with pertuzumab and docetaxel for the treatment of first-line MBC resulted in a PFS of 18.5 months [Baselga 2012b] which decreased to 9.6 months in second-line MBC as an antibody conjugate with mertansine [Verma, 2012] and further decreased to 6.2 months in subjects with at least 2 lines of anti-HER2-directed therapies for MBC [Wildiers, 2013].

1.1.3. Role of Lapatinib in the Treatment of Breast Cancer

1.1.3.1. Preclinical Evidence for Lapatinib

Lapatinib is a reversible, orally bioavailable small molecule tyrosine kinase quinazoline inhibitor (molecular weight (MW) 943) that inhibits both Epidermal Growth Factor Receptor (EGFR) and HER2. Lapatinib binds in the adenosine triphosphate (ATP) site and inhibits the tyrosine kinase activity located in the intracellular domains of HER2 and its co-receptor EGFR and the phosphorylation of both HER2 and EGFR are blocked [Wood, 2004]. Lapatinib inhibits cell proliferation and induces apoptosis by decreasing the downstream Mitogen-activated protein kinase (MAPK)/ Extracellular signal-regulated kinase (ERK) and the Phosphoinositide 3-kinase (PI3K)/AKT signal transduction pathways [Rusnak, 2001; Hegde, 2007]. Preclinical data demonstrated that lapatinib retained significant in vitro activity against HER2-positive cell lines selected for insensitivity to trastuzumab [Konecny, 2006]. Lapatinib is also effective in cases of trastuzumab resistance involving HER2 heterodimers, PTEN loss, or mutations in PIK3CA [O'Brien, 2010; Ghosh, 2007].

1.1.3.2. Lapatinib as Monotherapy

As first-line treatment for subjects with locally advanced or metastatic ErbB2-overexpressing breast cancer, single-agent lapatinib has resulted in a partial response (PR) rate and clinical benefit rate (CBR) (confirmed objective response at any time or stable disease for ≥24 weeks) of 24% and 31%, respectively [Gomez, 2006].

A Phase II study of single-agent lapatinib in 78 subjects with HER2-positive MBC with progressive disease on prior trastuzumab-containing regimens demonstrated a response rate of 5% and a CBR (complete response (CR)+PR+ stable disease (SD) ≥ 6 months) of 9% with a 15-week TTP and an OS of 79 weeks [Blackwell, 2009]. Tested in an even more heavily pretreated population (n=140) who had progressed on prior trastuzumab-containing regimens in addition to progression while receiving anthracyclines, taxanes, and capecitabine, response rates ranged between 1.4% to 4.3% by independent and investigator assessments, respectively. Approximately 6% of subjects, most (76%) of whom had received 4 or more lines of prior therapy, achieved clinical benefit in addition to a modest TTP of 9.1 weeks [Burstein, 2008]. Therefore, lapatinib monotherapy demonstrated early evidence of clinical activity in heavily pretreated, HER2-positive patients who had progressive disease on trastuzumab as well as cytotoxic therapy.

1.1.3.3. Lapatinib in Combination with Chemotherapy

EGF100151, a Phase III, randomized, open-label, multicenter study, compared lapatinib and capecitabine versus capecitabine in women with refractory advanced or metastatic breast cancer who had been treated with anthracyclines, taxanes, and prior trastuzumab therapy in the metastatic setting. Based on a blinded, independently reviewed analysis, the median TTP in the combination and single-agent arms, respectively, based on a blinded, independently reviewed analysis was 27.1 weeks and 18.1 weeks (HR = 0.57; 95% CI 0.43 to 0.77; p = 0.0001), with objective response rates (CR + PR) of 24% and 14%, respectively, by independent review (odds ratio [OR] = 1.9; 95% CI 1.1 to 3.4; p = 0.017) and 32% and 17%, respectively, by investigator-reported data (OR = 2.2; 95% CI 1.3 to 3.6; p = 0.002) [Geyer, 2006]. More recently, the clinical benefit of the lapatinib plus capecitabine regimen in second-line MBC and beyond was also demonstrated, with PFS rates of approximately 6 months, in comparison with TDM-1 [, 2012] and in comparison with trastuzumab in combination with capecitabine [Pivot, 2012]. Several smaller, nonrandomized studies of lapatinib in combination with other chemotherapies (i.e., vinorelbine, docetaxel, paclitaxel) have also demonstrated similar clinical efficacy in the setting of progression of disease on trastuzumab-based regimens [Di Leo, 2008; Cristofanilli, 2006; Jagiello-Gruzfeld 2009; LoRusso, 2008; Rezai, 2011]. Of note, in an exploratory analysis of study EGF100151, fewer subjects in the lapatinib plus capecitabine arm had CNS metastases as a first site of relapse during the study than in the capecitabine group. In this analysis, 4 (2%) subjects in the combination therapy group had symptomatic CNS progression as part of their first progression event as compared with 13 (6%) patients in the monotherapy group (p = 0.045) [Cameron, 2008]. Therefore, a body of evidence is amassing supporting the clinical utility of lapatinib following the progression of disease on trastuzumab-based therapies.

1.1.3.4. Lapatinib in combination with aromatase inhibitors

Lapatinib has been studied in combination with letrozole for the treatment of advanced or metastatic breast cancer in hormone receptor positive (estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) postmenopausal women.

EGF30008 was a randomised, double-blind, controlled trial in subjects with hormone-sensitive locally advanced or MBC, who had not received prior therapy for their metastatic disease. One thousand two hundred and eighty-six subjects were randomised to letrozole 2.5 mg once daily plus lapatinib 1500 mg once daily or letrozole with placebo. Randomization was stratified by sites of disease and prior adjuvant anti-estrogen therapy. HER2 receptor status was retrospectively determined by central laboratory testing. Of all subjects randomised to treatment, 219 subjects had tumors overexpressing the HER2 receptor (the 'HER2-positive population'), which was the pre-specified primary population for the analysis of efficacy. There were 952 HER2 negative subjects and a total of 115 subjects whose HER2 status was unconfirmed.

In the HER2-positive population, investigator-determined PFS was significantly greater with letrozole plus lapatinib compared with letrozole plus placebo (35.4 weeks [24.1; 39.4] versus 13.0 weeks [12.0; 23.7] and a HR= 0.71 [0.53, 0.96])

The benefit of lapatinib plus letrozole on PFS in the HER2-positive population was confirmed in a pre-planned Cox regression analysis (HR=0.65 [95 % CI 0.47-0.89] p=0.008). In addition to a PFS benefit seen in the HER2-positive subject population, combination therapy of lapatinib and letrozole offered an improvement in objective response rate compared with letrozole treatment alone (27.9% and 14.8% respectively) and in clinical benefit rate (47.7% and 28.7% respectively). At the time of the primary PFS analysis, the OS data analyzed included a limited number of events with less than half of the HER2-positive subjects having died. The corresponding HR was 0.77 (95% CI: 0.52, 1.14) and was not statistically significant. This study was the basis of the approval of lapatinib in combination with an aromatase inhibitor for the treatment of patients with hormone sensitive metastatic breast cancer.

1.1.4. Role of Dual blockade with Lapatinib and Trastuzumab in Treatment of Breast Cancer

1.1.4.1. Preclinical Mechanism

Preclinical data provided the scientific rationale for combining 2 HER2-targeted agents with unique and complementary mechanisms of action and potentially non-overlapping mechanisms of resistance. Certain mechanisms such as estrogen receptor (ER) signaling may attenuate the activity of both trastuzumab and lapatinib in HER2-positive cells [Wang, 2011]. Other mechanisms of resistance such as activation of the PI3K pathway [Dave 2011; O'Brien, 2010], levels of EGFR or HER3 [Ritter, 2007; Dua, 2010], expression of HER ligands [Ritter, 2007; Dua, 2010], and presence of carboxy terminal fragments of HER2 [Scaltriti, 2007; Xia, 2004], however, appear unique to either trastuzumab or lapatinib.

In addition, Dual blockade may enhance the effects of either single agent. Whereas lapatinib can inhibit the phosphorylation of HER3, likely through inhibiting the activation of HER2 dimerized with HER3 [Ritter, 2007], sustained inhibition of HER2 kinase activity with lapatinib has been shown to increase HER3 protein and phosphorylation levels. However, combined treatment with trastuzumab inhibited HER3 phosphorylation after sustained inhibition of HER2 by lapatinib [Garrett, 2011]. In other models, lapatinib exposure led to accumulation and stabilization of inactivated HER2 at the cell surface, which, in combination with trastuzumab, enhanced ADCC [Scaltriti, 2009; Maruyama, 2011].

Preclinical evidence has shown that combining these agents is synergistic, enhances anti-proliferative and apoptotic effects, and circumvents resistance to either agent alone [Konecny, 2006; Xia, 2005; O'Donovan, 2011]. Further supporting the complementary functions, the lapatinib plus trastuzumab combination achieved better blockade of the HER2 pathway and greater tumor inhibition than either agent alone [Rimawi, 2006; Rimawi, 2011].

In summary, the preclinical scientific rationale for the combination of lapatinib and trastuzumab is supported by the potentially non-overlapping mechanism of resistance, the complementary mechanisms of action, and the ability of each agent to enhance the activity of the other.

1.1.4.2. Clinical Efficacy of Dual blockade

1.1.4.2.1. Phase I Study EGF10023

The Phase I study in subjects with HER2-positive MBC determined the optimally tolerated regimen (OTR) of lapatinib in combination with trastuzumab. Early evidence of efficacy of the combination was observed in this study. This study was conducted in 2 phases: a dose-escalation phase to determine the OTR, and a pharmacokinetics (PK) phase to assess the potential for a drug-drug interaction when these 2 drugs are used in combination. All subjects (N=54) in study EGF10023 had HER2-positive MBC at study entry; almost half (44%) were ER- and progesterone receptor (PgR)-negative, and 50 of the subjects had received prior trastuzumab therapy. Concurrent administration of lapatinib (1000 mg) and trastuzumab did not result in significant alterations in the PK of either drug.

A total of 50 of the subjects were evaluable for clinical activity. As best response to treatment, CR was documented in 1 subject (1500-mg dose cohort) and PR in 7 subjects (2 in the 1250-mg dose cohort, 4 in the 1000-mg dose cohort, and 1 in the 750-mg dose cohort) for an ORR of 15%. Five of the 7 responding subjects required a dose reduction to a lower dose level during the course of study treatment. All subjects had received prior trastuzumab-containing regimens (median, 2 regimens [range, 1 to 6]). Overall, 6 subjects (11% of the overall population) had SD ≥6 months.

Dose-limiting toxicities (DLTs) were reported in 1 of 11 subjects enrolled in the lapatinib 1000-mg dose cohort, in 2 of 10 subjects enrolled in the 1250-mg dose cohort, and in 2 of 3 subjects enrolled in the 1500-mg dose cohort. As 2 out of 3 subjects experienced a DLT in the 1500-mg dose cohort, the OTR was exceeded at this combination dose

regimen. As a result, the 1000-mg and 1250-mg dose cohorts were considered in the determination of the OTR. Although the adverse event (AE) profiles and rates of DLTs were comparable between the 1000-mg and 1250-mg dose cohorts, the tolerability of the 1000-mg dose cohort was considered by the investigators to be more acceptable based on the constitutional symptoms (e.g., fatigue, arthralgia, anorexia, headache) experienced by the subjects in the 1250-mg dose cohort. As a result, the OTR was defined as 1000 mg lapatinib once daily with weekly trastuzumab (4 mg/kg intravenous [IV] loading dose followed by 2 mg/kg IV weekly).

All subjects in all dose cohorts experienced an AE during the study. AEs occurring in >20% of subjects in the 1000-mg dose cohort (n=38) were diarrhea (all grades 82%; Grade 3 was 13%), nausea (all grades 58%; Grade 3 was 3%), rash (all grades 58%; Grade 3 was 3%), fatigue (all grades 53%; Grade 3 was 11%), anorexia (all grades 39%; no Grade 3), and pruritis (all grades 24%; no Grade 3). The most common Grade 3 AEs were diarrhea (17%), fatigue (11%), and rash (6%). One of 3 (33%) subjects in the 1500-mg lapatinib cohort experienced a Grade 4 AE of hypokalemia. No Grade 5 or fatal AEs were reported.

Left ventricular ejection fraction (LVEF) was monitored in this study due to the potential for cardiac dysfunction. One subject in the 1500-mg dose cohort experienced asymptomatic reversible LVEF decline to 45% (echocardiogram [ECHO]) from a baseline value of 58% (multigated acquisition [MUGA]) and returned to baseline while still on therapy.

Concurrent administration of trastuzumab plus lapatinib was generally well tolerated, showed evidence of clinical activity in subjects who had progressed on prior trastuzumab therapy, and did not result in significant alterations in the PK of either drug. Therefore, these findings supported further exploration of the safety and activity of 1000 mg/day lapatinib plus trastuzumab in larger studies of subjects with HER2-positive MBC.

1.1.4.2.2. Phase III Study EGF104900 – Dual blockade in Metastatic Breast Cancer

Study EGF104900 was a randomized, open-label, multicenter, Phase III study designed to compare the efficacy and safety of lapatinib in combination with trastuzumab (Dual blockade) with that of lapatinib monotherapy in women with Stage IV, HER2-positive MBC who had received a prior trastuzumab-containing regimen in the metastatic setting. Upon radiologic evidence of disease progression on the lapatinib monotherapy treatment arm, subjects were allowed to cross over to receive treatment with Dual blockade.

The primary objective of the study was to compare investigator-assessed PFS in the Dual blockade arm with that in the lapatinib monotherapy arm, and secondary endpoints included a comparison of OS between the 2 treatment arms.

The eligibility criteria required subjects to have had at least 1 prior trastuzumab-containing regimen (trastuzumab plus cytotoxic chemotherapy or trastuzumab plus an anti-hormonal regimen) in the metastatic setting. Additionally, they must have had trastuzumab as their most recent regimen prior to study entry, with evidence of progressive disease on the most recent prior trastuzumab-containing regimen.

Subjects with either measurable disease or bone-only disease were randomized in a 1:1 fashion to either Dual blockade with lapatinib (1000 mg *per os* (orally) (PO) daily) plus trastuzumab (4 mg/kg IV load on Day 1 followed by 2 mg/kg weekly) or lapatinib (1500 mg PO daily) monotherapy. Randomization was stratified according to site of disease (visceral versus nonvisceral) and hormone receptor status (ER-negative and PgR-negative status versus ER-positive and/or PgR-positive status).

Study Population

The subject population had previous prolonged exposure to, and progression on, multiple cytotoxic chemotherapy- and trastuzumab-based regimens. The overall population had received a median of 6 prior anticancer regimens, 7 prior chemotherapies, and 3 prior lines of trastuzumab-containing regimens in the metastatic setting. Moreover, they must have had a trastuzumab-chemotherapy combination as their most recent treatment regimen prior to entering the study and must have had disease that progressed on this most recent prior trastuzumab-containing regimen.

Efficacy

PFS was statistically significant in favor of the Dual blockade arm, with an HR of 0.73 (95% CI 0.57 to 0.93; p = 0.008). The median PFS was longer in subjects who received Dual blockade treatment (12.0 weeks) compared with subjects who received monotherapy treatment (8.1 weeks) and was confirmed by independent review, with an HR of 0.71 (95% CI 0.52 to 0.98; p = 0.027) in favor of the Dual blockade arm. Median PFS by independent evaluation was 16.4 weeks and 11.1 weeks in subjects treated with Dual blockade and monotherapy treatment, respectively. Of note, for the 80% of subjects who had progressed on 2 or more lines of trastuzumab-containing regimens in the metastatic setting prior to study entry, there was a statistically significant improvement in PFS with Dual blockade (investigator-evaluated PFS, HR = 0.76; 95% CI 0.58 to 1.00; p = 0.041). Investigator-evaluated ORR was 10.3% in the Dual blockade arm and 6.9% in the lapatinib arm (OR=1.5; 95% CI 0.6 to 3.9; p = 0.4647), and investigator-assessed CBR (defined as a confirmed CR or PR at any time or SD for at least 24 weeks) was 24.7% in the combination arm and 12.4% in the monotherapy arm (OR = 2.2; 95% CI 1.2 to 4.5; p = 0.01) [Blackwell, 2010].

Final survival analysis, which included 291 subjects per their randomized treatment, regardless of crossover status, demonstrated a median OS of 14.0 months for the Dual blockade arm and 9.5 months for the monotherapy arm (N=291; HR=0.74; 95% CI 0.57 to 0.97; stratified log-rank p = 0.026) [Blackwell, 2012]. Additionally, there was a 10% improvement in the absolute OS rate at 6 months and a 15% improvement at 12 months for subjects who received Dual blockade treatment compared with subjects who received monotherapy treatment.

Data from exploratory analyses in the pivotal study showed an increased overall benefit for subjects with hormone receptor negative disease. The efficacy of the Dual blockade in terms of OS and ORR was increased in subjects with hormone receptor-negative tumors compared to those with hormone receptor-positive tumors, although the hazard ratios for PFS were similar (HR = 0.73 for both subgroups).

Safety

The most common AEs experienced in this study were diarrhea, nausea, rash, fatigue, and vomiting, and these events were similar in frequency between the lapatinib and Dual blockade arms with the exception of diarrhea (observed in 62% of subjects in the Dual blockade arm and 48% of subjects in the lapatinib monotherapy arm). Grade 3 or 4 diarrhea was reported in 8% of subjects in the Dual blockade arm and in 7% in the lapatinib monotherapy arm.

Non fatal serious adverse events (SAE)s were reported in 27% of subjects in the Dual blockade arm compared with 16% of subjects in the lapatinib arm. Decreased ejection fraction was the most frequent SAE (in 5% of subjects of the Dual blockade arm). No other SAEs were reported by more than 3% of subjects. Most subjects experienced SAEs in the Dual blockade arm that were not considered to be treatment-related by the investigator (8% versus 3% subjects for the Dual blockade and lapatinib monotherapy arms, respectively, had SAEs considered related to study treatment).

Five subjects experienced a fatal SAE. Two of these cases were due to progressive disease and 1 was attributed to aspiration pneumonia (Dual blockade arm), 1 to hepatorenal failure (lapatinib arm), and 1 to cardiac insufficiency (Dual blockade arm).

Per protocol, cardiac function was monitored every 12 weeks, and cardiac toxicity overall was low. While the frequency of cardiac events was higher in the Dual blockade treatment group (7% [n=11]) compared with the lapatinib monotherapy arm (2% [n=3]), most of the events were asymptomatic and resolved. Symptomatic cardiac events occurred in 3 subjects randomized to the Dual blockade arm, 1 subject in the lapatinib monotherapy arm, and 1 subject in the crossover arm. Of the 3 subjects in the Dual blockade arm, 2 recovered while 1 subject died of cardiac insufficiency in association with a suspected pulmonary embolism. Each of the subjects in the lapatinib monotherapy arm and in the crossover arm also recovered.

As lapatinib was present in both arms of the study, and consistent with the safety profile for lapatinib, diarrhea was the most common AE experienced in subjects treated with either Dual blockade or lapatinib monotherapy. More subjects experienced diarrhea with Dual blockade (62%, with 8% of subjects in the arm reporting Grade 3 or 4 events) compared with the lapatinib monotherapy arm (48%, with 7% of subjects in the arm reporting Grade 3 or 4 events). Most events resolved without adverse sequelae, and the majority (98%) of subjects in the Dual blockade arm were able to continue study drug without dose reductions. Study treatment interruptions due to diarrhea were reported in 10% of subjects in the Dual blockade arm and in 15% of subjects in the lapatinib monotherapy arm, and no subjects randomized to Dual blockade discontinued study drug due to diarrhea.

The overall number of hepatobiliary AEs was similar in both arms (11% and 9% respectively). Most hepatobiliary events were asymptomatic transaminase elevations that were infrequent and reversible upon treatment discontinuation; overall, there were few (4% [n=6] and 3% [n=5] for Dual blockade and lapatinib monotherapy, respectively) Grade 3 or 4 hepatobiliary AEs.

In summary, a statistically significant improvement in PFS and OS with dual blockade therapy compared with lapatinib monotherapy was demonstrated in these subjects who experienced progressive disease following multiple prior trastuzumab-containing regimens. This is the first study to demonstrate an OS benefit in this unique population of heavily pretreated subjects.

Additional subgroup analyses for OS showed that the magnitude of the benefit of Dual Blockade in subjects with hormone receptor-negative tumours [HR 0.62 (95% CI 0.42-0.90)] was greater than the benefit in subjects with hormone receptor-positive tumours [HR 0.84 (95% CI 0.58-1.23); although the hazard ratios for PFS were the same in both subgroups.

The results of EGF104900 were the basis for 2013 CHMP positive opinion and subsequent granting of marketing authorization from the European Medicines Agency (EMA) of dual blockade in the following indication: "*Lapatinib in combination with trastuzumab (Dual blockade) for adult patients with hormone receptor-negative metastatic breast cancer (MBC), whose tumors overexpress HER2 (ErbB2), that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy.*"

1.1.4.3. Dual blockade in the Neoadjuvant Setting

In the neoadjuvant setting, dual blockade has shown a higher rate of pathological complete response (pCR) given with or without concurrent chemotherapy compared with trastuzumab or lapatinib treatment. Several Phase II and Phase III clinical trials conducted in the neoadjuvant setting that randomized subjects to either dual blockade or either of their components have demonstrated the clinical utility of more complete HER2 receptor blockade utilizing the Dual blockade approach.

Study EGF106903, also known as the Neo-ALTTO study, was a randomized, open-label, multicenter, Phase III, neoadjuvant study enrolling 455 HER2-positive women with histologically confirmed invasive breast cancer [Baselga, 2012c]. Subjects newly diagnosed with Stages II or III primary breast cancer were randomized (1:1:1) to either a) Dual blockade with lapatinib (1000 mg PO daily) plus trastuzumab (4 mg/kg IV load followed by 2 mg/kg weekly) for 6 weeks, followed by lapatinib (750 mg PO daily) plus trastuzumab (2 mg/kg IV weekly) plus paclitaxel (80 mg/ meter squared (m^2) IV weekly) for an additional 12 weeks; b) trastuzumab alone (4 mg/kg IV load followed by 2 mg/kg weekly) for 6 weeks, followed by trastuzumab (2 mg/kg IV weekly) plus paclitaxel (80 mg/m^2 IV weekly) for an additional 12 weeks; or c) lapatinib alone (1500 mg PO daily) for 6 weeks, followed by lapatinib (1500 mg PO daily) plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks.

The proportion of subjects with pCR at surgery (defined as absence of invasive disease in the breast [Fisher, 1997; Fisher, 2002] was statistically significantly higher in the Dual blockade arm (51.3%) than in the trastuzumab arm (29.5%; p = 0.0001) with an overall OR of 2.62 (97.5% CI 1.50 to 4.58; p<0.001). The difference between the lapatinib arm (24.7%) and the trastuzumab arm (29.5%) was not statistically significant. Additionally, locoregional pCR (defined as absence of invasive disease in the breast and axilla) was

46.9% in the Dual blockade arm compared with 27.6% in the trastuzumab arm and 20.0% in the lapatinib arm (binomial p = 0.0007; OR = 2.40; p<0.001).

Another randomized, open-label, multicenter Phase III study (NSABP B-41) compared whether neoadjuvant Dual blockade or lapatinib increased pCR rate compared with trastuzumab [Robidoux, 2012]. Subjects enrolled in this study were randomized to receive doxorubicin (60 mg/m^2 q3weekly) in combination with cyclophosphamide (600 mg/m^2 q3weekly) for 4 cycles sequentially, followed by either Dual blockade (trastuzumab 4 mg/kg IV load followed by 2 mg/kg weekly plus lapatinib 750 mg PO daily) for 4 28-day cycles or trastuzumab or lapatinib (1250 mg PO daily), all 3 anti-HER2 regimens given concurrent with weekly paclitaxel (80 mg/m^2 on Days 1,8, and 15 of a 28-day cycle for 4 cycles).

pCR was achieved in the breast as well as locoregionally in the breast and axilla in 62% versus 52.5% (p = 0. 95) and 60.2% versus 49.4% (p = 0.056) of subjects, respectively, treated with Dual blockade compared with trastuzumab. There was no difference between lapatinib or trastuzumab, respectively (53.2% versus 52.5%, p = 0.99 breast only; 47.4% versus 49.4%, p = 0.78 breast and axilla).

Several additional smaller randomized, 3-arm translational studies have also been conducted as proof-of-principle studies for Dual blockade. Importantly, although not all of the Phase III studies achieved statistical significance, there is a consistent increase in the magnitude of pCR for treatment with Dual blockade when compared with the trastuzumab control.

Table 1 Overview of Pathologic Complete Response Rates

	Lapatinib	Trastuzumab	Lapatinib + Trastuzumab
pCR in breast and node[a], %:			
EGF106903 (Neo-ALTTO) [Baselga 2012c]	20	28	47
LPT109096	45	54	74
CHERLOB [Guarneri, 2012]	26	25	47
NSABP B41 [Robidoux, 2012]	47	49	60
pCR in breast[b], %			
EGF106903 (Neo-ALTTO) [Baselga 2012c]	25	30	51
LPT109096	52	54	74
CALGB 40601 [Carey, 2013]	32	40	51
NSABP B41 [Robidoux, 2012]	53	53	62

a. Defined as no invasive cancer in the breast and lymph nodes.
b. Defined as no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen

1.2. Study Rationale

1.2.1. Clinical Validity of Dual blockade

In the EGF104900 study population with heavily pretreated HER2-positive breast cancer, treatment with Dual blockade had a clinically meaningful OS benefit of 4.5 months yet a modest PFS improvement of approximately 1 month compared with lapatinib monotherapy. In an effort to further understand the apparent disconnect between a more modest PFS improvement with a clinically meaningful OS improvement, several additional analyses were undertaken to assess factors or biases that theoretically may have influenced the OS benefit and could account for this apparent disconnect. Of the factors evaluated, none were considered significant as to bias the OS benefit observed in EGF104900 thus no bias was identified.

Similar divergence of PFS and OS durations was reported in the large phase III Cleopatra [Baselga 2012a] and PHEREXA [Urruticoechea 2016] trials evaluating dual HER2 blockade (pertuzumab plus trastuzumab) in HER2-positive MBC.

Study EGF104900 demonstrated that in the population of HER2-positive subjects, Dual blockade can enhance blockade of the HER2 receptor in this heavily trastuzumab pretreated population. This effect driven by Dual blockade was both necessary and sufficient to provide a clinically meaningful OS benefit, even in the absence of cytotoxic therapy.

1.2.2. HER2-Enriched Population for Study EGF117165

The application of whole transcriptome profiling to classical breast cancer clinical subtypes has unravelled substantial biological complexity. Gene expression profiles revealed inherent structure that clustered breast cancers into 4 distinct, primary breast cancer subtypes—luminal A, luminal B, HER2-enriched, and basal-like—and a normal-like group. Analyses of breast cancers by intrinsic molecular subtype demonstrated significant differences in terms of risk factors, baseline prognoses, and responses to systemic therapies [Perou, 2000; Sorlie, 2001; Parker, 2009].

The Prediction Analysis of Microarray (PAM) is a classifier algorithm used to assign breast cancers to 1 of the 4 intrinsic molecular subtypes noted above. The assignment of a breast cancer to a molecular subtype is based on the expression of 50 genes that were derived from an initial list of 1906 intrinsic genes identified by whole transcriptome microarray analyses. As indicated above, prototypic tumor samples representative of classical clinical breast cancer molecular subtypes (i.e., ER-positive or ER-negative tumors, HER2-positive or HER2-negative tumors, triple-negative), in addition to tissue from normal breast samples, were used in the development of the classifier algorithm and refinement of the intrinsic gene signature to a minimized set of 50 (PAM50). PAM50 has been developed as an *in vitro* diagnostic using the Nanostring nCounter analysis platform. The commercial name of the PAM50 assay is Prosigna. The intended in vitro diagnostic use of the assay is to assess a breast cancer patient's risk of distant recurrence

at 10 years. For this purpose, the standardized test has received Food and Drug Administration (FDA) 510(k) clearance.

Determination of HER2 status in breast cancer using standard immunohistochemistry (IHC)/fluorescence in situ hybridization (FISH)-based methods not only provides prognostic information to a patient but also is a standard-of-care requirement for patients to receive treatment with HER2-directed agents. Of note, the HER2-enriched subtype signature includes 2 genes on the chromosome 17q12-21 amplicon: HER2 and GRB7 [Parker, 2009]. In a comprehensive retrospective molecular analysis of >400 banked breast tumors, only 50% of clinically HER2-positive tumors were classified as the HER2-enriched subtype by PAM50 assay [Cancer Genome Atlas Network, 2012]. Retrospective analyses have shown that the HER2 enriched subtype correlated with enhanced clinical outcome when treated with trastuzumab in the early breast cancer setting [Prat 2014, Glück 2012; Gomez Pardo, 2011].

In the aforementioned CALGB 40601 neoadjuvant study in clinically HER2-positive early breast cancer, 33% of the evaluable samples were HER2 enriched compared to 33% luminal A, 22% luminal B, 7% basal-like, and 6% normal-like subtypes. In a prospective analysis of pCR rates by breast cancer subtype, HER2-enriched tumors has the highest rate of pCR (75%) regardless of anti-HER2 therapy used in combination with paclitaxel. In those found to be HER2 enriched, pCR rate for the Dual blockade arm was 89% compared to 40% in Luminal A35% in Luminal B; and 50% in basal-like subgroups. In the setting of a constant chemotherapy backbone across all treatment arms, higher pCR rates were observed in the HER2-enriched subtype, supporting the use of this assay in defining those subjects whose disease may be more dependent on the HER2 pathway and consequently exquisitely sensitive to the effects of HER2-directed therapy.

A prospective clinical trial in the metastatic setting evaluating clinical outcome of anti-HER2 therapy by PAM50 or Prosigna assigned breast cancer molecular subtype has not been reported. Nevertheless, it has been recognized that subjects with HER2 positive disease derive differential benefit from anti-HER2 blockade. Based on the neoadjuvant data discussed above, classification into the HER2 enriched subtype may predict enhanced as well as prolonged benefit to anti-HER2 directed therapy. In fact, gene expression analyses in primary tumors of a prematurely closed trial of single anti-HER2 therapy in first line metastatic setting showed that the HER2-enriched subtype identified a group of subjects with longer time on protocol compared to the non-HER2-enriched subtype [Montemurro 2013]. Additionally, in the heavily pre-treated HER2 population as defined in this study, HER2-enriched tumors might represent those strongly driven by the HER2 pathway and as such could derive the most benefit from enhanced blockade of the HER2 receptor in the absence of chemotherapy. In order to avoid any real or perceived lack of clinical equipoise when randomizing subjects in EGF117165 to a trastuzumab chemotherapy combination versus the non-cytotoxic based Dual blockade, the randomized portion of EGF117165 will target those subjects with breast cancer that is not only HER2 positive by standard clinical definitions, but is also HER2-enriched as defined by the Prosigna assay.

A prospective clinical trial in the metastatic setting evaluating clinical outcome of anti-HER2 therapy using the "HER2 enriched" definition has not been reported. Additionally, the benefit of dual blockade from the EGF104900 study was seen in the intent-to-treat (ITT) population which included all HER2 positive subjects as defined by standard histopathologic criteria. At this time, there is a lack of knowledge regarding any molecular mechanism(s) that might modulate response in a HER2 enriched population compared to a standard defined HER2 positive population. Therefore, this study will also enroll standard HER2 positive subjects as defined by standard histopathologic criteria with a non-HER2 enriched subtype that will be assigned to treatment with lapatinib in combination with trastuzumab.

1.2.3. Immunomodulation by dual blockade as a putative mechanism affecting response to subsequent lines of therapy.

Chemotherapies traditionally produce cytotoxic effects that translate into reduction in tumor burden, resulting in a significant measurable effect. The development of novel targeted agents for solid tumors, with mechanisms of action that produce effects that differ from those traditionally measured in clinical studies, have been described for immunomodulatory and epigenetic-targeted agents [Wolchok, 2009]. These differences in on-treatment effects could, in part, explain modest PFS gains while subjects may gain a more prolonged benefit from subsequent therapy, which may ultimately translate to an OS advantage.

The EGF104900 study population was heavily pretreated, with a median of 6 prior chemotherapeutic agents; as is standard in the treatment of breast cancer, the types of agents received were of different mechanistic classes (e.g., taxanes, anthracyclines, and alkylating agents). The chemotherapy-free period during which subjects received treatment with Dual blockade in EGF104900 may have reversed resistance to chemotherapy, thus conferring the disease sensitive to subsequent anticancer therapy.

There is now mounting evidence that a pre-existing immunologic response might enhance the effects of conventional cytotoxic chemotherapy and HER2 targeted therapy in early HER2+ breast cancer [Denkert 2010, Issa-Nummer 2013, Denkert 2015, Ignatiadis 2012, Loi 2013, Loi 2014] and anti-HER2 therapies seem to be able to engage the immune system in different ways. For instance, pre-clinical data suggest that Lapatinib enhances T-cell and IFN-γ-based immunity and affects the myeloid infiltrate (i.e. tumor-associated macrophages and monocytes) in tumors [Hannesdóttir 2013, Laoui 2013]. Emerging data from the neoadjuvant setting provide useful insights on molecular changes induced by HER2-targeted neoadjuvant treatment and recent studies are suggesting that single HER2 targeted agents and Dual blockade of the HER2 receptor induce changes in immune markers and the tumor microenvironment [Bianchini 2016, Dieci 2015]. The Neosphere trial showed that HER2 targeted agents and dual HER2 blockade modulate the amount of tumor infiltrating lymphocytes (TIL) - a surrogate biomarker of pre-existing host antitumour immunity - and the expression levels of selected mRNA immune markers [Bianchini 2016]. The investigators were also able to show that these patient-level immune modulations are linked to distant event free survival and the differential changes in stromal TILS (sTIL) levels actually seem to carry more prognostic information than either pre-or post-treatment sTIL levels.

Tumors with increased numbers of TIL after treatment may be able to elicit an antitumor immune response and may have a particularly strong response to subsequent treatment lines, as the immune cells may have been already sensitized against some tumor antigens before the onset of chemotherapy and therefore enhance the ability of chemotherapy to eliminate cancer cells. Immunomodulation by dual HER2 blockade is a plausible mechanism how molecular changes could help to overcome resistance to chemotherapeutic agents, eventually leading to increased clinical activity and augmented response seen in overall survival.

The primary hypothesis under evaluation in this study is that the chemotherapy-free period during which subjects receive treatment with Dual blockade modulates the immune microenvironment, which in turn may influence the efficacy of sequential treatment. A recent study just revealed a comparable distribution and composition of infiltrating lymphocyte subtypes in metastasis when compared to the matched primary tumor [Sobottka 2016]. This pattern was found regardless of the anatomical site at which the metastasis had occurred, suggesting that primary tumor shapes the infiltrating immune cell composition rather than the metastases with their local immunity [Sobottka 2016]. The EGF11765 study will support a better understanding if the rapidly accumulating evidence for the importance of the immune microenvironment in HER2-positive breast cancer and the observed immunomodulation in the neoadjuvant setting can be confirmed in the advanced setting and support the putative mechanism of action of HER2 dual blockade and its potential function on the tumor microenvironment.

1.2.4. Hypothesis

It is postulated that treatment with Dual blockade (lapatinib in combination with trastuzumab) may cause molecular changes that may sensitize tumors to subsequent post-study therapies. As discussed above, based on emerging data the focus will be on immunomodulation markers. The primary endpoint of the study will be to evaluate changes in expression of biomarkers associated with immunomodulation.

This Phase II study will evaluate potential mechanisms related to immunomodulation to explore the antitumor activity of dual blockade and gain insight into the observed post-study treatment effect on survival in EGF104900. In addition, it will provide a descriptive clinical outcome for subjects treated with trastuzumab in combination with lapatinib or chemotherapy.

1.3. Benefit: Risk Assessment

Dual blockade demonstrated a statistically significant benefit in PFS compared with lapatinib monotherapy in study EGF104900, with a median PFS of 12.0 weeks for subjects who received dual blockade compared with 8.1 weeks for subjects who received lapatinib alone. This translated into a 28% reduction in the risk of progression or death for subjects who received dual blockade relative to subjects treated with lapatinib monotherapy.

The median overall survival (OS) was substantially longer in subjects who received dual blockade (14 months) compared with those who received lapatinib monotherapy (9.5

months); the hazard ratio was 0.74. There was a 10% improvement in absolute OS rate at 6 months and a 15% improvement at 12 months for subjects who received dual blockade compared with subjects who received lapatinib monotherapy.

Although all subjects benefited from dual blockade, the magnitude of the benefit of dual blockade in subjects with hormone receptor-negative tumors was greater than the benefit in subjects with hormone receptor-positive tumors. The median PFS for the hormone receptor negative subgroup was 15.3 weeks and the median overall survival for this population was 17.2 months. HER2-positive, hormone-receptor negative tumors predominantly have the HER2-enriched molecular subtype.

This benefit was demonstrated in a population of subjects with previous prolonged exposure to, and progression on, multiple cytotoxic chemotherapy and trastuzumab-based regimens.

1.3.1. Risk Assessment

This section outlines the risk assessment and mitigation strategy for this protocol.

Summaries of findings from both clinical and nonclinical studies conducted with lapatinib can be found in the Investigator's Brochure (IB) and product label.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Study Treatments		
Hepatobiliary `events	Lapatinib has been associated with a low incidence of hepatotoxicity (<1%). In EGF104900, the overall number of hepatobiliary events was similar in both arms (11% and 9% respectively), and the incidence of Grade 3 or 4 events did not increase by the addition of trastuzumab to lapatinib [Blackwell 2012]. Additionally, most hepatobiliary events were asymptomatic transaminase elevations that were infrequent and reversible upon treatment discontinuation. Consistent with this, in EGF104900 no hepatobiliary abnormalities met the criteria for Hy's Law. This rate was comparable to the rate observed for lapatinib monotherapy (8% reported hepatobiliary adverse events compared to 3% in the placebo arm) in the adjuvant breast cancer setting in EGF105485 (TEACH) [Goss 2013]. Certain chemotherapies are also associated with a risk for hepatotoxicity.	Liver function will be monitored every 3 weeks during treatment. Hepatic SAE definition and LFT monitoring/stopping rules added to protocols. These instructions are comparable to those included in the prescribing information.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Study Treatments		
Cardiac events (decreased LVEF)	HER2 targeted agents are associated with decreased LVEFs. The rate of LVEFs was numerically higher in the dual blockade arm (6% incidence of LVEF AEs) compared to the lapatinib monotherapy arm (2% incidence of LVEF AEs) in EGF104900. Most of the cardiac SAEs were asymptomatic and reversible events of decreased ejection fraction. The frequency of cardiac events was higher in the dual blockade treatment group (7%) compared with 2% in the lapatinib group in EGF104900. This is consistent with the established safety profiles of lapatinib and trastuzumab.	Routine monitoring of LVEF every 12 weeks. Cardiac SAE definition and monitoring rules added to protocols. Comparable instructions included in prescribing information.
Diarrhea	Diarrhea is a recognised AE associated with tyrosine kinase inhibition. Diarrhea is one of the most commonly reported AEs with lapatinib treatment. More subjects experienced diarrhea with Dual blockade (62%, with 8% of subjects reporting Grade 3 or 4 events) compared with the lapatinib arm (48%, with 7% of subjects reporting Grade 3 or 4 events) in EGF104900. Diarrhea was generally manageable with standard treatments and resolved without dose interruption.	Implementation of diarrhea management guidelines in the protocol.
Rash	Rash/skin toxicity is a recognized adverse event associated with tyrosine kinase inhibition and more profoundly with TKi that target EGFR. This toxicity is a common AE with lapatinib and trastuzumab treatment. The incidence of rash did not increase with the addition of trastuzumab to lapatinib. In EGF104900, 35 subjects (23%) in the Dual blockade arm and 43 subjects (29%) in the lapatinib arm experienced rash. With the exception of one Grade 3 rash event in the lapatinib arm, all events of rash were Grade 1 or 2 and did not lead to SAEs or require withdrawal of a subject from the study.	Implementation of rash management guidelines in the protocol.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Study Treatments		
Nausea/vomiting	Nausea/vomiting are known effects of small-molecule tyrosine kinase inhibitors and certain types of chemotherapy. The incidence of nausea was 28% for each arm in EGF104900. The incidence of nausea and vomiting varies by the type of chemotherapy used in combination with trastuzumab.	Routine safety assessments every 3 weeks will monitor for these effects.
Myelosuppression /Neutropenia	Chemotherapy is associated with myelosuppressive effects including neutropenia. Incidence rates vary with the combination of different chemotherapies with trastuzumab. There were few cytopenias in EGF104900 which studied Dual blockade in the absence of chemotherapy.	Routine monitoring for hematological abnormalities will be conducted every 3 weeks
Study Procedures		
Biopsy	Complications of a biopsy include pain (typically mild), haemorrhage; infection; adverse response to anesthesia; pneumothorax and/or pleural effusion	Subject may be required to lie flat for several hours following the procedure to control bleeding. Pain can be managed with small amounts of narcotics.
Abbreviations: AE, adverse event; ; LFT, liver function test; LVEF, left ventricular ejection fraction; SAE, serious adverse event.		

1.3.2. Benefit Assessment

A subject enrolled to trastuzumab in combination with lapatinib will have the potential benefit of receiving an active anti-HER2 therapy without the associated toxicities of chemotherapy. Subjects enrolled to trastuzumab in combination with chemotherapy of the investigator's choice will receive treatment with the common clinical practice of continuation of trastuzumab in combination with chemotherapy.

Subjects enrolled in the study will contribute to the process of developing new therapies in this area of unmet medical need as well as contribute to the understanding of the evolution of a tumor as it disseminates from the primary tumor and is treated in the metastatic setting with HER2-based therapy including trastuzumab.

In addition, the biopsy of a metastatic site provides potential data to inform the investigator on the treatment of the subject's metastatic disease. As the HER2 and hormone receptor status of a metastatic site may diverge from the primary breast cancer

sample, confirmation of HER2 and hormone receptor status is recommended by European Society for Medical Oncology (ESMO) guidelines. Loss of HER2 expression would severely limit the efficacy of subsequent anti-HER2 therapies. Likewise, loss of hormone receptor status would make the patient unlikely to benefit from endocrine therapy with an aromatase inhibitor.

1.3.3. Overall Benefit: Risk Conclusion

Lapatinib is a tyrosine kinase inhibitor that is indicated in the treatment of MBC. The scientific rationale for combination treatment with lapatinib and trastuzumab is robust. Lapatinib in combination with trastuzumab has been shown to prolong PFS and reduce the risk of death by 26% in women with HER2-positive breast cancer who have been previously treated with trastuzumab and chemotherapy.

Both hormone receptor-positive and hormone receptor-negative subjects benefited from Dual blockade. However, the benefit of Dual blockade was not limited to the subjects with hormone receptor-negative disease in EGF104900 or HER2 enriched in a neoadjuvant study with Dual blockade [Carey, 2013]. Therefore, a more complete blockade of HER2 via the combination of lapatinib and trastuzumab should control this disease in the absence of chemotherapy regardless of breast molecular subtype.

Cumulative safety data for lapatinib demonstrate that identified risks include hepatobiliary events, cardiac events (decreased LVEF), interstitial lung disease/pneumonitis, diarrhea, rash, nausea/vomiting, and neutropenia. The majority of these events are class effects associated with tyrosine kinase inhibitors. The ICF will communicate the identified/potential risks associated with the study. Specific monitoring and guidance in the protocol will manage these risks as has been done in other studies.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate changes in the expression of biomarkers associated with immunomodulation.	• Changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated with immunomodulation between the pre-treatment biopsy and disease progression biopsy. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately.
Secondary	
• To describe ORR, CBR, and PFS on study treatment in subjects treated with trastuzumab in combination with lapatinib or chemotherapy. • To explore association between changes in biomarkers and PFS. • To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy.	• Investigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months • Describe if a change at disease progression in biomarker correlates with PFS. • Summary AE profile for both treatment arms
[redacted]	

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CR, complete response; HER, human epidermal growth factor receptor; [redacted] PD, progressive disease; PFS, progression-free survival;PR, partial response; ORR, overall response rate; SD, stable disease.

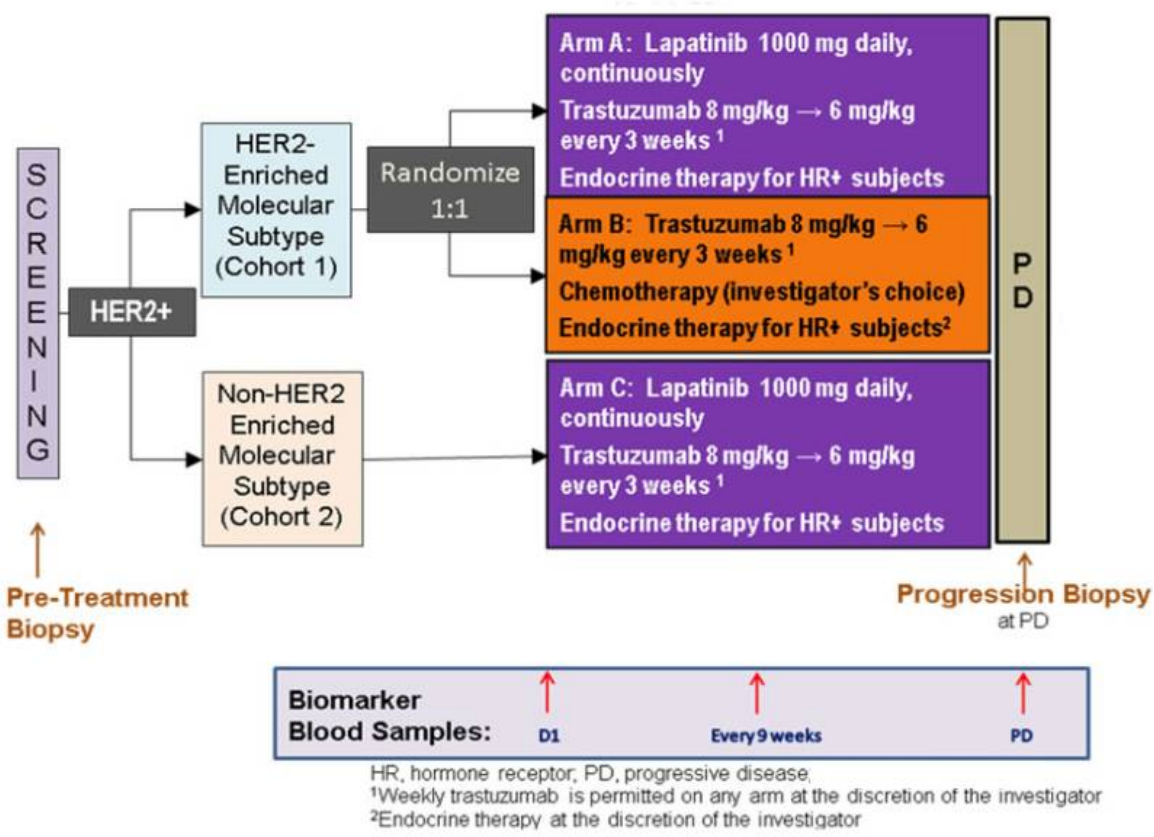
3. STUDY DESIGN

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 9), are required for study conduct.

This is a Phase II, 3 arm, open-label study (See Figure 1 for study schema). The subject population is subjects with HER2-positive metastatic breast cancer who received at least two prior regimens containing trastuzumab in the metastatic setting. The last regimen must have included trastuzumab plus chemotherapy. The molecular subtype of a biopsy of a metastatic site will be centrally determined by the Prosigna assay. HER2 and hormone receptor status will be centrally determined. Subjects with centrally determined HER2 positive disease will be allocated to one of two cohorts depending on the molecular subtype of their biopsy:

- **COHORT 1 - HER2-Enriched** contains HER2+ subjects with a HER2-enriched molecular subtype. Subjects with HER2-enriched molecular subtype will be randomized 1:1 to either:
    - **ARM A - Trastuzumab in combination with lapatinib**: lapatinib 1000 mg PO once daily plus trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV q3weekly. Weekly trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly is acceptable at the discretion of the investigator. Subjects with hormone receptor (ER and/or PgR)-positive, HER2-positive MBC randomized to this arm will be required to be treated with an aromatase inhibitor of the investigator's choice.
    - **ARM B - Trastuzumab in combination with chemotherapy**: trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV q3weekly plus chemotherapy of the investigator's choice. Weekly trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly is acceptable at the discretion of the investigator. An aromatase inhibitor may be used for hormone receptor-positive, HER2-positive subjects at the discretion of the investigator.
- **COHORT 2 - Non-HER2-Enriched** contains HER2+ subjects with luminal A, luminal B and basal-like molecular subtypes
    - Subjects in the Non-HER2 enriched cohort will be assigned to a third arm: **ARM C - Trastuzumab in combination with lapatinib**: lapatinib 1000 mg PO once daily plus trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV q3weeks. Weekly trastuzumab (loading dose of 4 mg/kg) followed by maintenance dose of 2 mg/kg IV weekly is acceptable at the discretion of the investigator. Subjects with hormone receptor (ER and/or PgR)-positive, HER2-positive MBC randomized to this arm will be required to be treated with an aromatase inhibitor of the investigator's choice.

Figure 1 Study Schema



Biopsies of a metastatic site will be collected at two timepoints: screening (pre-treatment) and at disease progression (progression). The primary objective is to evaluate changes in biomarkers associated with immunomodulation, between the pre-treatment biopsy and the progression biopsy within each arm. Radiologic disease assessments will be performed every 9 weeks until 54 weeks then every 24 weeks thereafter until disease progression, death, or withdrawal from study treatment for any reason (e.g. unacceptable toxicity). [redacted]

Safety assessments including physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs and weight, adverse event (AE) monitoring, and laboratory tests (complete blood count, blood chemistry including liver function test) will be done at screening and then every 3 weeks for the duration of therapy. Additional safety assessments, such as cardiac monitoring, are required for all subjects every 12 weeks until discontinuation from the study therapy.

All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal of consent or any other reasons mentioned in section 4.2.1.

In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.
Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

The data cut-off for the primary analysis will be defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier. Following the cut-off date for the primary analysis, the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study
- At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.

Due to difficulty in enrolling subjects into this trial, future enrolment will be halted and the study will be terminated early.

At the time of stopping the enrollment, the sponsor will notify all the investigators in writing. Subjects who have signed consent prior to receipt of the written notification, if determined eligible for a cohort (HER2-enriched or Non-HER2-enriched) will be permitted to continue in the study.

The term ‘study treatment’ is used throughout the protocol to generally describe the combination of products or individual products under evaluation in this protocol. When referring to specific compounds or one combination, the compound names or other designation will be used.

Refer to Section 5.8 for guidelines for adverse events of special interest and dose modifications and Section 5.9.1 for liver stopping criteria.

Subject completion is defined in Section 4.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety including the biopsy and blood specimen collection procedures.

3.1. Discussion of Design

This study is a post-approval commitment with regulatory authorities. It is designed with the primary endpoint to evaluate the changes in biomarkers associated with immunomodulation between the pre-treatment and disease progression biopsy.

Subjects will undergo a biopsy at screening (pre-treatment biopsy) that will be used to determine the breast cancer molecular subtype of the tumor. HER2 and hormone receptor status will be centrally determined on the pre-treatment biopy, tumors that are HER2-enriched have features that suggest they are more likely to be dependent on HER2 signaling and in effect may modulate pathways that differ from tumors that are not HER2-enriched. Therefore, two cohorts will be utilized in this study, a HER2-enriched cohort and Non-HER2-enriched cohort. A prospective clinical trial in the metastatic setting evaluating clinical outcome of anti-HER2 therapy using the "HER2 enriched" definition has not been reported. Additionally, the benefit of dual blockade from the EGF104900 study was seen in the ITT population which included all HER2 positive subjects as defined by standard histopathologic criteria. At this time, there is a lack of knowledge regarding any molecular mechanism(s) that might modulate response in a HER2 enriched population compared to a standard defined HER2 positive population. Therefore, this study will also enroll a standard HER2 positive population as defined by standard histopathologic criteria with non-HER2-enriched subtype that will be assigned to treatment with lapatinib in combination with trastuzumab. Both cohorts will be treated with dual blockade (trastuzumab in combination with lapatinib). The inclusion of these two cohorts was discussed and agreed upon with the scientific advice working party of the Committee for Medicinal Products for Human Use (CHMP).

3.1.1. Use of 3-weekly trastuzumab dosing

The initial studies leading to the approval of trastuzumab in HER2-positive metastatic breast cancer (MBC), utilized a weekly dosing schedule for trastuzumab of 4 mg/kg, followed by 2 mg/kg [Vogel, 2002; Cobleigh, 1999, Slamon, 2001]. This was based on the hypothesis that trastuzumab had an elimination half-life ($t_{½}$) of 6 days. However, data have subsequently shown that trastuzumab $t_{½}$ is closer to 28 days, which led to the 3-week dosing schedule of 8 mg/kg, followed by 6 mg/kg [Bruno, 2005].

The efficacy of the 3-weekly dosing schedule has been clinically validated in several studies. A Phase II study evaluated the safety and efficacy of trastuzumab given every 3 weeks in combination with paclitaxel as first- or second-line treatment for metastatic breast cancer (MBC) [Leyland-Jones, 2003]. In this open-label study of trastuzumab-naive subjects with HER2-positive MBC, the mean trastuzumab $t_{½}$ ranged from 18-27 days, and reached steady-state levels at approximately Cycle 8 (i.e. Week 24). Serum trough levels for the 3-week dosing were similar to the regulatory approved monotherapy trastuzumab weekly regimen [Cobleigh, 1999], exceeded the minimum targeted trough

level of 20 μg/mL prior to administration of the second cycle of therapy, and were subsequently higher with continued treatment (50.1 μg/mL Cycle 4; 72.3 μg/mL Cycle 12). This regimen was thought to be efficacious with a reported objective response rate of 59%. This compares favourably with the rate of 41% observed with trastuzumab administered weekly with paclitaxel administered every 3 weeks as first-line treatment of HER2-positive MBC in a randomized study [Slamon, 2001], and also with a rate of 57% observed in a non-randomized Phase II study of weekly trastuzumab in combination with weekly paclitaxel [Seidman, 2002].

Similarly, Baselga and colleagues confirmed this finding in a Phase II study of trastuzumab monotherapy dosed every 3 weeks given as first-line treatment for HER2-positive MBC [Baselga, 2005]. The average exposure on the 3 week schedule at any given time was comparable with weekly dosing schedules. The mean trough levels exceeded 27 μg/mL at Cycle 2 and increased to approximately 50 μg/mL by Cycle 6. The cumulative dose was identical between the 2 scheduling regimens. Additionally, efficacy did not seem to be altered, as the study reported 23% response rate for centrally confirmed HER2-positive disease, similar to the response rate of 15% observed in the weekly trastuzumab monotherapy trial [Cobleigh, 1999].

The trastuzumab Summary of Product Characteristics recommends administration on a weekly schedule (4 mg/kg initial loading dose, then 2 mg/kg thereafter) for MBC and either a weekly or q3weekly (8 mg/kg initial loading dose, then 6 mg/kg thereafter) schedule for early breast cancer [Trastuzumab Summary of Product Characteristics, 2013]. The q3weekly schedule, however, has been incorporated in many clinical trials for MBC. In the adjuvant setting, clinical studies of adjuvant trastuzumab with chemotherapy utilized both the weekly and 3-weekly trastuzumab dosing schedules [Romond, 2005; Piccart-Gebhart, 2005], and reported no difference between either disease free survival DFS or OS. Therefore, dosing scheduling of trastuzumab was demonstrated to have no impact on efficacy. Furthermore, the q3weekly schedule is more convenient for subjects, as it reduces the number of infusions received as well as the number of visits to the clinic.

As such, subjects will be allowed to use either the weekly trastuzumab dosing schedule or the q3weekly trastuzumab dosing schedule at the discretion of the investigator.

3.1.2. Endocrine and HER2-Directed Therapy for Hormone-Receptor Positive, HER2-Positive MBC

Preclinical and clinical evidence supports that more complete HER-2 blockade occurs with the use of both lapatinib in combination with anti-estrogen therapy to avoid escape of upregulation of the estrogen receptor. As a result, endocrine therapy with an aromatast inhibitor of the investigator's choice will be mandated for the lapatinib trastuzumab treatment arm.

The benefit of combining endocrine with an aromatase inhibitor and HER2-targeted therapy in the treatment of HER2-positive MBC has been demonstrated in 2 Phase III randomized studies. Lapatinib in combination with letrozole demonstrated a statistically significant improvement in investigator-evaluated PFS compared with

letrozole plus placebo (HR = 0.71; 95% CI 0.53 to 0.96; stratified log-rank p = 0.019), indicating a 29% reduction in risk of disease progression. Median PFS in this first-line setting was 35.4 weeks (95% CI 24.1 to 39.4) compared with 13.0 weeks (95% CI 12.0, to 23.7), respectively [Johnston, 2009].

In the Phase III TaNDEM trial, anastrozole was compared with anastrozole plus trastuzumab as first-line treatment for postmenopausal women with HER2-positive, hormone receptor-positive MBC. The combination of anastrozole plus trastuzumab treatment doubled median PFS from 2.4 months to 4.8 months (approximately 10 weeks to 21 weeks; (anastrozole compared with combination treatment, respectively), with a HR of 0.63 (95% CI 0.47 to 0.84; log-rank p = 0.0016) [Kaufman, 2009].

Investigators will choose the aromatase inhibitor administered to subjects in the trastuzumab-lapatinib combination arm. Premenopausal subjects with hormone receptor-positive disease should receive ovarian ablation/suppression (luteinizing hormone-releasing hormone analogue, surgery or ovarian irradiation) in combination with an aromatase inhibitor (AI). Postmenopausal subjects should receive an AI of the investigator's choice. As in clinical practice, third generation AIs are used interchangeably and are perceived to be equivalent by the clinicians.

The drug interaction potential of the AIs has been reviewed in literature [Lonning, 2003]. Based on the pharmacokinetics of lapatinib and the AIs the only relevant mechanisms for a potential interaction would involve metabolism mediated by CYP3A4. There is no evidence that the AIs interact with ABC transporters. Based on assessment of available data, the potential for drug-drug interactions between lapatinib and AI is very low. There are no apparent pharmacokinetic considerations related to the combined therapeutic use of these agents.

The combination of Dual blockade with aromatase inhibitors and tamoxifen was studied in the ALTTO (EGF106708) trial. As of February 2014, all subjects have completed treatment and no pharmacovigilance safety signal has emerged.

3.1.3. Biomarkers and the Timing of Tumor Biopsies

This study will have tumor biopsies taken at screening (pre-treatment biopsy) and at disease progression (progression biopsy) to analyze biomarkers associated with immunomodulation potentially connected to an impact on the response to chemotherapy (see Section 1.2.3). The primary endpoint will evaluate changes in these biomarkers measured in the progression biopsy compared to the pre-treatment biopsy.

Analysis of these candidate biomarkers in pre-treatment tumor tissue and at disease progression may provide indicative information on immunomodulation, as an effect of treatment.

The site of the pre-treatment biopsy and progression biopsy should remain the same if possible. CNS and bone biopsies are excluded organs.

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Since the initiation of this trial, the enrollment has been poor due to lack of interest by investigators and patients. Therefore, future enrolment will be halted and the study will be terminated early. Up to 31 Jul 2016, 29 patients have been enrolled.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on study treatment that may impact subject eligibility is provided in the IB/IB supplement, product label for lapatinib [TYVERB™ Package Leaflet, 2015], the study procedures manual (SPM), and the product labels for trastuzumab, paclitaxel, docetaxel, *nab* paclitaxel, capecitabine, gemcitabine, and vinorelbine [Herceptin Package Insert, 2014; Xeloda Package Insert, 2006; Abraxane Package Insert,2005; Gemzar Package Insert, 2007; Taxotere Package Insert, 2004;Taxol Package Insert, 2000; Navelbine Package Insert, 2002].

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Signed written informed consent
2. Female ≥18 years
3. Histologically or cytologially confirmed invasive breast cancer with distant metastasis
4. Subjects must have at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [Eisenhauer, 2009]

   Note: Biopsied lesions should not be used as target lesions.
5. Documentation of HER2 overexpression or gene amplification, in the invasive component of either the primary tumor or metastatic disease site as defined as:

   - 3+ by IHC

   and/or

   - HER2/neu gene amplification by fluorescence, chromogenic, or silver in situ hybridization [FISH, CISH or SISH;≥6 HER2/neu gene copies per nucleus or a FISH, CISH, or SISH test ratio (HER2 gene copies to chromosome 17 signals) of ≥2.0 OR HER2/chromosome 17 ratio ≤2.0 with average HER2 copy number ≥6 signals/cell nucleus];

6. Centrally determined HER2-positive, hormone receptor status, breast molecular subtype by PAM50 on the pre-treatment biopsy of metastatic lesion obtained during screening

   Note: Biopsied lesions should not be used as target lesions.

7. Progression on at least 2 lines of anti-HER2-targeted therapies for MBC
8. Documented radiological disease progression during the most recent treatment regimen for metastatic disease
9. Most recent treatment regimen for metastatic disease must include trastuzumab and chemotherapy.

   Note: Trastuzumab emtansine (T-DM1) is considered acceptable as prior trastuzumab/chemotherapy regimen

10. Agreement to provide 2 tumor biopsies
11. Prior treatment with pertuzumab, lapatinib, and/or trastuzumab emtansine is allowed; however, the last treatment for MBC must not include trastuzumab in combination with pertuzumab.
12. Subjects with radiographically stable CNS metastases, defined as radiographically stable on the previous 2 brain imaging scans, asymptomatic, and off systemic steroids and anticonvulsants for at least 1 month are eligible; treatment with prophylactic anticonvulsants is permitted unless listed under Prohibited Medications (Section 6)
13. Discontinuation of all prior chemotherapy, immunotherapy, or biological therapy at least 3 weeks prior to the first dose of study treatmentis required.

    Note: Discontinuation of trastuzumab is not necessary.

14. All treatment related toxicities, except alopecia, must have recovered to Grade 1 or better (Common Terminology Criteria for Adverse Events (CTCAE); version 4.0) prior to administration of the first dose of study treatment.
15. Baseline LVEF ≥50% as measured by ECHO or MUGA and above the testing institution's lower limit of normal
16. QTc <450 msec *or* QTc <480 msec for patients with bundle branch block. The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual overread.

    For subject eligibility and withdrawal, QT correction formula QTcB will be used.

    For purposes of this data analysis, Bazett's formula will be used as the primary method of calculating the corrected QT interval. The QTc should be based on either a single ECG or an average of 3 sequential ECGs obtained within 24 hours of each other.
    The QTc should be based on single or averaged QTc values of triplicate ECGs obtained over a brief recording period.

17. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study treatment and agree to use effective contraception, as defined in Section 7.4.7, during the study and for 30 days following the last dose of study treatment.
18. ECOG performance status of 0 or 1 (Section 12.3)
19. Completion of screening and baseline assessments
20. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
21. At least 4 weeks must have elapsed since the last surgery and 2 weeks must have elapsed since radiotherapy
22. Adequate baseline organ function as defined in Table 2

Table 2 Baseline Laboratory Values

Screening laboratory values should be used to confirm subject eligibility. Laboratory results may be retested if necessary to confirm eligibility.

SYSTEM	LABORATORY VALUES
Hematologic[1]	
ANC	$\geq 1.5 \times 10^9$/L
Hemoglobin	≥9.0 g/dL (after transfusion if needed)
Platelets	$\geq 100 \times 10^9$/L
Hepatic	
Albumin	≥2.5 g/dL
Serum bilirubin	≤1.25 x ULN[2]
AST and ALT	≤2.5 × ULN
Renal	
Calculate creatinine clearance[3]	≥40 mL/min

1. These values must be independent of growth factor support and stable for at least one week post transfusion.
2. With the exception of those subjects who have Gilbert's syndrome; the bilirubin in these subjects should be at their baseline
3. Calculated by the Cockcroft and Gault method. (Refer to Appendix 9 for more details)

Abbreviations: ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.1.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Lactating female

   Note: Women with potential to have children must be willing to practice acceptable methods of birth control during the study

2. Bone-only disease and/or disease that cannot be biopsied.
3. Unstable CNS metastases or leptomeningeal carcinomatosis not considered radiographically stable (as defined above in inclusion criterion 12)

   Note: Subjects with radiographically stable central nervous system (CNS) metastases are defined as radiographically stable on the previous 2 brain imaging studies, asymptomatic, and off systemic steroids and anticonvulsants for at least 1 month; treatment with prophylactic anticonvulsants is permitted unless listed under Prohibited Medications

4. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions including concurrent disease that could interfere with subject's safety, obtaining informed consent, or compliance with the study procedures.
5. Serious cardiac illness or medical condition including but not confined to:
   - Uncontrolled arrhythmias (e.g. ventricular tachycardia, high-grade atrioventricular (AV)-block, supraventricular arrhythmias which are not adequately rate-controlled);
   - Angina pectoris requiring antianginal medication;
   - History of congestive heart failure or systolic dysfunction (LVEF <50%);
   - Documented myocardial infarction <6 months from study entry;
   - Evidence of transmural infarction on ECG;
   - Poorly controlled hypertension (e.g. systolic >160mm Hg or diastolic >100mm Hg);
   - Clinically significant valvular heart disease.
6. Current active hepatic or biliary disease (with exception of subjects with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment)
7. Any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels as well as subjects with ulcerative colitis are also excluded
8. Any prohibited medication as described in Section 6.2

9. Prior treatment with trastuzumab in combination with lapatinib or prior treatment with an irreversible inhibitor of the intracellular domain of the HER2 receptor such as neratinib
10. Last treatment for metastatic disease including trastuzumab in combination with pertuzumab
11. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment
12. A known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to any of the study drugs or their excipients that, in the opinion of the investigator or medical lead, contraindicates participation

French subjects must not have participated in any study using an investigational drug during the previous 30 days.

4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Discontinuation Criteria for patient studies if any of the following criteria are met:

- QTc >500msec
- Uncorrected QT >600msec
- Change from baseline: QTc > 60 msec*

  These criteria should be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study.

  *This criterion is optional but should be strongly considered based on local regulatory requirements.

  For subjects with underlying Bundle Branch Block:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450msec	>500msec
450-480msec	≥530msec

Subjects will receive study treatment until disease progression, death, withdrawal of consent or any other reasons mentioned in this section, including unacceptable adverse event (as well as meeting stopping criteria for liver chemistry defined in Section 5.9 or for hematologic and other non-hematologic toxicity).

Study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated
- Subject's own request for reasons other than those above

All subjects who may require permanent discontinuation of 1 of the 2 study treatment products in a given treatment combination must discontinue both study treatment products in that combination.

In addition, study treatment will be discontinued if the sponsor discontinues the study due to safety reasons.

The primary reason for permanent discontinuation of study treatment must be clearly documented in the subject's medical record and recorded in the electronic case report form (eCRF).

All subjects who discontinue from study treatment due to an AE or any other reasons other than disease progression will have safety and efficacy assessments performed until disease progression, new anticancer therapy, death, withdrawal or until the end of study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression) as specified in the Time and Events table (Table 9) and results documented in the eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event' will be recorded as the primary reason for permanent discontinuation on the CRF. Once a subject permanently discontinues study treatment, the subject will not be allowed to be retreated.

Subjects with abnormal clinical or laboratory findings that are believed to be treatment-related will be followed until the condition resolves or until laboratory findings are not considered clinically significant.

Refer to details regarding liver chemistry abnormalities and withdrawal as specified in Section 5.9.1.

In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued

for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.

4.2.2. Subject Withdrawal from Study

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time.

Subjects will also be withdrawn from the study if there is a major deviation(s) from the protocol that occurred by the investigator or by the subject, without obtaining prior consent of Novartis.

If the subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the relevant evaluations – please refer to Section 7 “Time and Events Schedule” (Table 9) for complete details. Data are to be recorded in the eCRF. Subjects with abnormal clinical or laboratory findings that are believed to be treatment related will be followed until the condition resolves or until laboratory findings are not considered clinically significant.

If any of the trial subjects are lost to follow-up prior to subject completion, contact will initially be attempted through the trial research nurse and the lead investigator at each centre. Where these attempts are unsuccessful, the subject’s doctor should be contacted and asked to contact the subject or her/his family and provide follow-up information to the recruiting centre. It is only after at least 3 attempts to contact have been unsuccessful, that a subject may be declared “Lost to follow-up”. Subjects declared lost to follow-up that resume their visits should be followed as per the protocol schedule of assessments.

4.2.3. Subject Completion

A subject will be considered to have completed the study if the subject presents with disease progression, starts a new anti-cancer therapy, dies or withdraws from the study, or the study ends, whichever comes first. Document the cause of completion in the eCRF.

A subject will be considered to have withdrawn from the study if the subject has not experienced disease progression and is lost to follow-up, has withdrawn consent, or has withdrawn at the investigator's discretion.
All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal of consent or any other reasons mentioned in section 4.2.1. In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.

Data collection will continue until a subject has completed or discontinued the study.

4.3. Screening/Run-in Failures

A subject is considered to be a screen/baseline failure if the subject signs the informed consent form but withdraws before enrolment in treatment arm, or does not meet all inclusion and exclusion criteria. All potential subjects who are screened for enrollment in this study including screening/baseline failures will be listed on the Subject Screening Log/Identification List. Reasons for exclusion will be recorded for potential subjects who do not enter the study.

5. STUDY TREATMENTS

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. When referring to specific compounds or one combination, the compound names or other designation will be used.

5.1. Study Treatment and Reference Therapy

5.1.1. Lapatinib

Commerically packed supplies or non-commerical lapatinib is supplied as 250-mg orange tablets that are oval, biconvex, and orange film-coated with 1 side plain and the opposite side debossed with FG HLS. Each tablet contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet. As additional formulations of lapatinib become available, equivalent doses of the new formulation can be used. For more information regarding the physical and chemical properties of the drug substance and list of excipients, refer to the lapatinib summary of product characteristics [Lapatinib Summary of Product Characteristics, 2015].

Lapatinib will be provided to sites by Novartis. The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, study treatmentis not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available upon request.

Adequate precautions must be taken to avoid direct contact with the investigational product. The occupational hazards and recommended handling procedures are provided in the MSDS.

5.1.1.1. Lapatinib Dosage and Administration

- Lapatinib will be dispatched to the site only after receipt of required documents in accordance with applicable regulatory requirements and Novartis procedures. Only subjects enrolled in the study may receive lapatinib, in accordance with all

applicable regulatory requirements. Only the site pharmacist or authorized site personnel may supply or administer lapatinib therapy.

- Lapatinib will be dispensed to the subject on the first day of treatment, after it has been confirmed that the subject meets all eligibility criteria and all baseline and screening assessments have been completed and the results reviewed. Subjects will receive their re-supply of lapatinib therapy at the time of a scheduled visit.

- Study staff will carefully instruct subjects on how to take lapatinib and the correct dose to take. For example, subjects randomized to the lapatinib plus trastuzumab arm are to receive 1000 mg per day of lapatinib, so will be instructed to take 4 x 250 mg tablets once daily. Subjects must take lapatinib either 1 hour (or more) before a meal or 1 hour (or more) after a meal (for example, 1 hour before or 1 hour after breakfast each day). Lapatinib is taken continuously. A record of therapy administered to each subject must be maintained in the source documents (see Section 5.7).

- Lapatinib dose modification guidelines are outlined in Section 5.2 and should be used for the management of treatment-related toxicities. Subjects should be carefully instructed when any dose modifications occur.

- **NOTE: Lapatinib should <u>NOT</u> be taken with grapefruit or grapefruit juice. Grapefruit and grapefruit juice is not permitted for the duration of the study.**

- *If a subject vomits after taking lapatinib, the subject should be instructed <u>not</u> to retake the dose. Subjects should take the next scheduled dose of lapatinib therapy. If vomiting persists then the subject should contact the investigator. However, if the tablets are clearly visually found after the vomiting incident then, in this circumstance, the dose may be repeated.*

5.1.2. Trastuzumab

Trastuzumab [Herceptin 2014] is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Excipients in each vial include: L-histidine hydrochloride, L-histidine, trehalose, and polysorbate 20, USP. Reconstitution with sterile water for injections for 150mg single-dose use vial or Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative for 440mg multi-dose vial, yields a solution containing 21mg/mL trastuzumab, at approximately pH 6.

Refer to Trastuzumab Product Information [Herceptin 2014] for additional details.

Trastuzumab will be sourced locally from commercial stock. Investigators are responsible for ensuring that subjects receive supplies of trastuzumab for the entire duration of the study, except in countries where Regulatory Authorities mandate that the Sponsor must supply all study treatment(s) required for study participation. The contents of the label will be in accordance with all applicable regulatory requirements.

5.1.2.1. Trastuzumab Dosage and Administration

Trastuzumab will be administered on Day 1 of the start of lapatinib or in conjunction with the first cycle of chemotherapy, as an 8 mg/kg loading dose. Subsequently, trastuzumab will be administered q3weekly as a 6 mg/kg maintenance dose. At the discretion of the investigator, weekly trastuzumab can be given in either of the three treatment arms (loading dose 4mg/kg followed by weekly administration of 2mg/kg). Trastuzumab is administered by intravenous infusion and a ± 3-day window is allowed for scheduling for Day 1 of each cycle. Dose reduction of trastuzumab is not allowed in this study. Specific guidelines in case of dose delay of trastuzumab are outlined in Section 5.8.2 and should be used for the management of treatment-related toxicities.

5.1.3. Chemotherapy

The specific chemotherapy used will be at the discretion of the investigator based on previous treatment and subject status at the time of study entry.

Please note that Trastuzumab emtansine (T-DM1) is not acceptable as a trastuzumab/chemotherapy regimen for Arm B.

Typical chemotherapies used in this setting are described below. However, the chemotherapy that could be used is not limited to these chemotherapies and is the choice of the investigator

5.1.3.1. Paclitaxel

Paclitaxel Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous (IV) infusion. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor EL (polyoxythylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. Paclitaxel is generally available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials individually packaged in a carton. Refer to the product label for information regarding the physical and chemical properties of paclitaxel [Taxol Package Insert 2000].

5.1.3.2. Docetaxel

Docetaxel is supplied as a viscous solution containing 40 mg/mL docetaxel in single-dose vials containing 20 mg or 80 mg of docetaxel in 0.5 mL or 2.0 mL polysorbate 80, respectively. The concentrate for infusion (parenteral preparation to be diluted) will be accompanied by solvent (13% ethanol in water for injection). Refer to the product label for information regarding the physical and chemical properties of docetaxel [Taxotere Package Insert, 2004].

5.1.3.3. *Nab* paclitaxel

Nab paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% sodium chloride injection, USP prior to IV solution. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human

albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Nab paclitaxel is free of solvents. Refer to the product label for information regarding the physical and chemical properties of *nab* paclitaxel [Abraxane Package Insert, 2005].

5.1.3.4. Capecitabine

Capecitabine is supplied as a biconvex, oblong, light peach and peach colored, film-coated tablet for oral administration. Each light peach colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. Each tablet contains inactive ingredients including anhydrous lactose, croscarmellose sodium, hydroxpropyl methylcellulose, microcrystalline cellulose, magnesium sterate. The film coating contains hydroxpropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides. Refer to the product label for information regarding the physical and chemical properties of capecitabine [Xeloda Package Insert, 2006].

5.1.3.5. Gemcitabine

Gemcitabine is supplied in a sterile form for IV use only. Each single-use vial contains either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Reconstituted dilutions yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder. Reconstituted gemcitabine is a clear, colorless to light straw-colorless solution. Refer to the product label for information regarding the physical and chemical properties of gemcitabine [Gemzar Package Insert, 2007].

5.1.3.6. Vinorelbine

Vinorelbine Injection is a clear, colorless to pale yellow solution in water for injection containing 10mg vinorelbine tartrate per mL. Vinorelbine Injection is supplied in single-use, clear glass vials as a sterile, non-pyrogenic aqueous solution with no preservatives or other additives present; 10mg/1mL and 50mg/5mL single-use vials are available. All dosing of vinorelbine is expressed as the free base and not the ditartrate salt (for example, a 50mg dose = 69mg of the salt). All vials are labelled in terms of the free base. Refer to the product label for further information regarding the physical and chemical properties of vinorelbine [Navelbine Package Insert, 2002].

5.1.3.7. Chemotherapy Dosage and Administration

The choice of chemotherapy agent will be at the discretion of the treating investigator. Refer to Table 3 for details on administration (recommended dose and schedule, route, and duration of treatment) of each chemotherapy agent. A record of the chemotherapy agent administered to each subject must be maintained in the source documents (refer to Section 5.5 for details on product accountability).

Table 3 List of Common Chemotherapy Dose and Schedule

Chemotherapy	Recommended Dose	Route	Recommended Schedule
paclitaxel[1]	80 mg/m^2	IV	Days 1, 8, and 15 of a 28-day cycle
docetaxel[1]	75 mg/m^2	1h IV	Day 1 of a 21-day cycle
nab paclitaxel	100 mg/m^2	30-min IV	Days 1, 8, and 15 of 28-day cycle
capecitabine	2000 mg/m^2 as two equal, divided doses administered 12h apart (morning and evening)[2]	PO	Days 1 – 14 of a 21-day cycle
gemcitabine	1250 mg/m^2	30-min IV	Days 1 and 8 of a 21-day cycle
vinorelbine	20 mg/m^2	10-min IV	Days 1, 8, and 15 of a 21-day cycle

1. refer to Section 5.1.3.8 for information on pre-medication for paclitaxel and docetaxel administration.
2. morning and evening doses of capecitabine must be taken with food or within 30 minutes after food with approximately 200mL of water.

Abbreviations: h=hour; IV=intravenous; PO=orally.

5.1.3.8. Premedication for Paclitaxel and Docetaxel Administration

Investigators may use their discretion (local standard of care) with regard to administration of pre-medications for paclitaxel and docetaxel treatment (e.g., oral instead of IV pre-medication permitted where available, administering day before and day of paclitaxel administration, etc.). Investigators must document exactly what was given, dates, and route of administration on the 'Concomitant Medications' eCRF. Please note, dexamethasone is a prohibited medication above 1.5 mg (refer to Section 6.2). Additionally, cimetidine, if given in place of ranitidine, is only permitted as a pre-medication and should not be given on a continuous basis.

All pre-medications administered prior to paclitaxel and docetaxel infusion will not be supplied for this study.

Additional information will be in the study procedures manual.

5.1.4. Endocrine Therapy with Aromatase Inhibitors

The endocrine therapy with an aromatase inhibitor is chosen at the discretion of the investigator. All subjects in one of the two arms treated with trastuzumab in combination with lapatinib are required to be treated with a concomitant aromatase

inhibitor. The aromatase inhibitor chosen by the investigator at randomization must remain the same throughout the study. Refer to product information for recommended doses and instructions regarding dose delays [Aromasin 2008; Arimidex, 2009; Femara 2010].

Endocrine therapy with an aromatase inhibitor will be administered on Day 1 of study treatment. Dose reductions for AIs are not permitted.

5.2. Dose Adjustments

At each clinic visit, subjects will be evaluated for evidence of study drug-related (lapatinib, trastuzumab, endocrine therapy or chemotherapy agent) toxicity. Results of laboratory assessments must be reviewed prior to the administration of study treatment.

5.3. Handling and Storage of Study Treatment

Lapatinib and trastuzumab must be stored in a secure area under the appropriate physical conditions for the product. Sites must maintain a temperature log for lapatinib. Access to and administration of lapatinib will be limited to the investigator and authorized site staff. Lapatinib must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Unused study treatment will be destroyed at site.

5.4. Treatment Assignment

Subjects will be assigned to study treatment in accordance with their molecular subtype. The HER2-enriched cohort will be randomized to treatment with either combination regimen with equal probability. The Non-HER2-enriched cohort will be assigned to treatment with trastuzumab in combination with lapatinib (Dual blockade).

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

Upon completion of all the required baseline and screening assessments, eligible subjects will be registered into the Interractive Response Technology (IRT) system by the investigator or authorized site staff. To randomize the subject in the HER2 enriched cohort, the study staff will enter the subject number into the IRT to obtain a randomization number and treatment group assignment. Study staff must also enter data for HER2 Non-enriched subjects. Subject numbers must be entered into the system and although this cohort will not be ‘randomized’ and assigned a treatment group, non-enriched subjects will receive a ‘randomization’ number. Confirmation will be received at the site on the completion of transaction. Study-specific instructional worksheets will be provided for the use of the IRT.

Subjects in the HER2-enriched cohort will be centrally randomized using a randomization schedule generated by the Biostatistical Department, which will assign subjects in a 1:1 ratio to either trastuzumab in combination with lapatinib or

chemotherapy of the investigator's choice. Once a randomization number has been assigned it must not be re-assigned even in cases of errors.

5.5. Blinding

This is an open-labeled study.

5.6. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of study treatment dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

5.7. Treatment Compliance

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

Lapatinib

Compliance with lapatinib will be assessed through querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of lapatinib tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF. Redispensing of lapatinib is not allowed unless extreme circumstances exist (i.e. hurricane; flood; etc) and approval is granted by the medical lead.

Trastuzumab

Trastuzumab will be intravenously administered to subjects at the study site. Administration will be documented in the source documents and reported in the eCRF. Compliance with trastuzumab treatment will be collected and recorded in source documents and in the eCRF on the Trastuzumab Exposure page including dates of administration and dates of treatment delays.

5.8. Dose Delays and Modifications

Study treatment will be administered until disease progression or death or discontinuation of study treatment due to unacceptable toxicity or other reasons (i.e. consent withdrawal, non-compliance). At each study visit, subjects will be evaluated for evidence of study treatment-related adverse events. The severity of adverse events will be graded utilizing the CTCAE 4.0 [NCI 2009]. Subjects should be carefully instructed on how to take study treatment if any dose modifications occur. If a subject permanently discontinues

any one of the study treatments, then the subject must be permanently withdrawn from all study treatment.

Recommendations for study treatment delays due to hematologic and chemistry toxicities are found in Table 4. For recommendations for lapatinib administration due to lapatinib-related adverse event, refer to Section 5.8.1; recommendations for trastuzumab administration due to trastuzumab-related adverse events refer to Section 5.8.2; and for recommendations for AI administration please refer to Section 5.8.3. Delays for chemotherapy should follow normal practice guidelines and package inserts.

Table 4 Study Treatment Delays for Hematology and Chemistry Toxicities

Toxicity	
• Hematology	• ANC is $<1.0 \times 10^9$/L • Platelet count is $<75.0 \times 10^9$/L • Hemoglobin is <9.0 g/dL
• Chemistry	• Unresolved Grade 3 or 4 toxicity (except liver chemistry) • For liver chemistry stopping and follow-up criteria, refer to Section 5.9
• Calculated Creatinine Clearance[1]	• ≤40 mL/min

1 Calculated by the Cockcroft and Gault Method.

5.8.1. Lapatinib

A delay in the administration of lapatinib for no more than 2 weeks is allowed for resolution of adverse events according to the criteria summarized in Table 5, except in the event of left ventricular cardiac dysfunction, interstitial pneumonitis, or hepatoxicity (Refer to Section 5.8.4, and Section 5.9 for further details). If treatment is delayed for reasons other than adverse events (i.e., unplanned travel or vacation, or lack of transportation to the site) and the subject has insufficient drug supply available, the subject should resume the usual dosing schedule once drug supply is available. However, if the subject has been off lapatinib for more than 2 weeks, the investigator must consult the medical lead prior to resuming therapy.

For subjects that are receiving lapatinib plust trastuzumab, one dose reduction of lapatinib to 750 mg is permitted according to the criteria defined in Table 5. If a subject permanently discontinues lapatinib for any reason, then re-initiation of lapatinib treatment is not permitted. The medical lead must be consulted prior to implementing any change in dosing not listed above.

Table 5 Recommendations for Lapatinib Administration due to Lapatinib-related Adverse Events

Adverse Event (NCI CTCAE Grade[1])	Action to be Taken
Grade 1 or Grade 2 (excluding Grade 1 or Grade 2 diarrhea with complicating features, cardiac events, and hepatobiliary events)	**Continue** lapatinib***** • If prolonged duration (≥2 weeks) of Grade 2 event occurs which affects the subject's QoL, **one dose reduction** of lapatinib by 1 tablet (250mg) to 750 mg is permitted ***Refer to the Supportive Care Guidelines** in the SPM for uncomplicated diarrhea and skin-related adverse events.
Grade 1 or Grade 2 diarrhea with complicating features **Grade 3 or Grade 4** (excluding Grade 3/ Grade 4 interstitial pneumonitis, Grade 4 rash, symptomatic cardiac events, and hepatobiliary events)	**Delay** lapatinib until resolution to ≤Grade 2 without complicating features***** • If the AE recurs and lapatinib dose was 1000 mg at time of recurrence, dose reduce 1 tablet (250mg) to 750 mg • If the AE recurs and lapatinib dose was 750mg at the time of recurrence, either discontinue or consult with the medical lead • If AE does not resolve to ≤Grade 2 (within 2 weeks from last administration), consult with the medical lead ***Refer to the Supportive Care Guidelines** in the SPM for diarrhea and skin-related adverse events.
Grade 3 or Grade 4 interstitial pneumonitis[2] Grade 4 rash manifested as toxic epidermal necrolysis (i.e., Stevens Johnson's Syndrome, etc)	**Permanently discontinue** lapatinib and treat as clinically appropriate
Cardiac Events	Refer to Section 5.8.4 for criteria on lapatinib administration following cardiac events
Hepatobiliary Events (Any Grade)	Refer to Section 5.9 for lapatinib dose modification for liver chemistry stopping and follow-up criteria
Hematologic Toxicities	Refer to Table 4

1. Severity Grade of AE according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v4.0 NCI 2009
2. Refer to Section 5.8.4 for treatment recommendations when subjects present with symptoms of interstitial pneumonitis or cardiac events.

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; AE, adverse event; QoL, quality of life

5.8.2. Trastuzumab

Trastuzumab may be delayed or discontinued for adverse events.

Dose interruption: Trastuzumab may be held for a maximum of 6 weeks. If the trastuzumab-related adverse event does not recover to ≤ Grade 2 after 6 weeks, discontinue trastuzumab. If trastuzumab dosing is delayed more than 6 weeks for reasons other than trastuzumab-related adverse events, the medical lead must be contacted.

Trastuzumab loading dose: Administration of trastuzumab occurs on a weekly or 21-day cycle, and may be delayed for up to 7 days for adverse events without the requirement of a re-loading dose.

For the 21 day cycle, a re-loading dose of 8 mg/kg must be used if more than 28 days have elapsed from the last administered trastuzumab dose, followed by the usual maintenance dose of 6 mg/kg/IV q3-weekly thereafter.

For the weekly cycle, a re-loading dose of 4 mg/kg must be used if more than 14 days have elapsed from the last administered trastuzumab dose, followed by the usual maintenance dose of 2 mg/kg/IV weekly thereafter.

Dose discontinuation: The recommendation to continue, delay or permanently discontinue trastuzumab due to adverse events is summarized in Table 6. If trastuzumab treatment is discontinued, then all study treatments in that must be discontinued.

Table 6 Recommendations for Trastuzumab Administration due to Trastuzumab-related Adverse Events

Adverse Events (NCI CTCAE Grade[1])	Action to be Taken
Non-hematologic Grade 1 or Grade 2 (excluding cardiac events)	**Continue** trastuzumab
Non-hematologic Grade 3 or Grade 4 (excluding cardiac events, interstitial pneumonitis)	**Delay** trastuzumab until recovery to ≤Grade 2 (maximum hold up to 6 weeks) If AE does not resolve to ≤Grade 2 after 6 weeks, discontinue trastuzumab
Grade 3 or Grade 4 interstitial pneumonitis[2]	**Permanently discontinue** trastuzumab and treat as clinically appropriate (refer to Section 5.8.4)
Hypersensitivity reactions	Refer to Section 5.8.2.1
Cardiac Events	Refer to Section 5.8.4 for criteria on trastuzumab administration following cardiac evaluations
Hematologic Toxicities	Refer to Table 4

1. Severity Grade of AE according to NCI CTCAEv4.0 [NCI 2009]
2. Refer to Section 5.8.4 for treatment recommendations when subjects present with symptoms of interstitial pneumonitis or cardiac events

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; AE, adverse event; QoL, quality of life)

5.8.2.1. Trastuzumab Dose Recommendations for Hypersensitivity Reactions

Subjects with extensive pulmonary disease e.g. lymphangitis, multiple metastases, recurrent pleural effusions, and those with pre-existing respiratory compromise may be at increased risk for serious hypersensitivity reactions.

The decision to administer or discontinue trastuzumab in the event a subject presents with hypersensitivity reaction is summarized in Table 7.

Table 7 Dose Delay Recommendations for Trastuzumab-related Hypersensitivity

Hypersensitivity Reaction	Action
Life threatening reaction (e.g. tachypnea, bronchospasm, hypotension, hypoxia)	**Permanently discontinue** trastuzumab
Severe or moderate reaction	Slow or stop the trastuzumab infusion Provide supportive care with oxygen, beta agonists, antihistamines or corticosteroids Subject may be retreated with trastuzumab Pre-medication with corticosteroids, antihistamines and antipyretics may be used before subsequent trastuzumab infusions
Moderate or mild reaction	Treat with antipyretics and antihistamines Re-treat with trastuzumab next dose

5.8.3. Aromatase Inhibitor (AI) of Investigator choice

There will be no dose reductions for any of the three of the AIs (letrozole, exemestane, or anastrozole). Please hold any of the three AIs for any Grade 3 or 4 drug related toxicities. If the subject experiences any hematologic toxicity, refer to Table 4.

If a subject is required to stop treatment with the AI for more than 7 days, the medical lead must be consulted.

5.8.4. Criteria for Evaluating Cardiac and Respiratory Events

Asymptomatic cardiac events:

Subjects who have a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline, and the ejection fraction is below the institution's lower limit of normal, should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving trastuzumab and/or lapatinib. This event must be reported as an SAE (see Section 7.4.2.4).

If the repeat ejection fraction evaluation confirms a ≥20% decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's lower limit of normal, then study treatment should be temporarily discontinued.

If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the medical lead, the subject may be restarted on trastuzumab. Subjects receiving lapatinib may be restarted at a reduced dose by 250mg (lapatinib dose of 750mg). For such subjects, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after re-challenge, and then every 4 weeks thereafter.

If repeat ejection fraction evaluation still shows a decrease ≥20% in left ventricular ejection fraction relative to baseline, and the value is below the institution's lower limit of normal, then the subject should be withdrawn from trastuzumab and/or lapatinib. Ejection fraction should continue to be monitored every four weeks for at least 16 weeks or until resolution.

Refer to SPM for cardiac safety algorithm detailing asymptomatic cardiac event assessment and follow up.

Symptomatic cardiac events:

Subjects with an NCI CTCAE grade 3 or 4 LVEF decrease must be withdrawn from study treatment.

Interstitial pneumonitis:

Subjects with an NCI CTCAE Grade 3 or 4 interstitial pneumonitis must be withdrawn from study treatment and must be reported as an SAE.

QTc Abnormalities

QT/QTc interval Prolongation:

Discontinuation Criteria for patient studies if any of the following criteria are met:

- QTc >500msec
- Uncorrected QT >600msec
- Change from baseline: QTc > 60 msec*

  These criteria should be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study.

  *This criterion is optional but should be strongly considered based on local regulatory requirements.

  For subjects with underlying Bundle Branch Block:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450msec	>500msec
450-480msec	≥530msec

When any QT/QTc stopping criteria are met, in addition to discontinuation of study treatment, do the following:

- Close and adequate ECG monitoring should be performed, confirm with additional ECGs that the interpretation is correct (along with manual overreading)
- Obtain consultation from cardiologist
- Check and supplement electrolytes (e.g., magnesium, calcium, potassium).
- Check and consider to stop co-administration of other medicine(s) known to cause QT prolongation
- Check and consider other factors that may contribute to QT prolongation, e.g., active ischemia, congestive heart failure (CHF), congenital long QT syndrome, etc.

5.8.5. Criteria for Evaluating Dermatologic Adverse Events

Significant skin adverse events (Grade 3 or more) resulting from lapatinib are rare (1-3%). Please refer to Section 12.8 for full guidance on evaluation of skin adverse reaction, follow-up including lapatinib holding and stopping rules as well as general guidance on treatment options.

If any NCI-CTCAE Grade 4 dermatologic event occurs, lapatinib must be permanently discontinued.

For NCI-CTCAE Grade 3 dermatological reactions, or a Grade 2 dermatological reaction which is not improved after 2 weeks with recommended management strategies, a brief (up to 14 days) therapy interruption is recommended; the daily dose of lapatinib should then be reinstated. In some cases, the skin event may improve without the need for interrupting therapy with lapatinib.

It is strongly recommended that subjects who develop dermatological reactions receive evaluations by a consultant dermatologist for management on the specific side effect.

A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines and immunomodulators, and hypoallergenic moisturizers and emolliens for dry skin. Please refer to Section 12.8.5 for full guidance on the treatment of skin adverse reaction.

NOTE: if revisions are made between protocol amendments, the most updated version is included in SPM.

5.8.6. Criteria for Evaluating Gastrointestinal Adverse Events

If GI adverse events are not appropriately managed, they may be associated with the development of dehydration. Management of gastrointestinal adverse events is discussed in detail in Appendix 7 Section 12.7.

NOTE: if revisions are made between protocol amendments, the most updated version is included in SPM.

5.8.6.1. Nausea and Vomiting

In subjects who have emesis and are unable to retain lapatinib and/or other oral medication, every attempt should be made to obtain control of nausea and vomiting. If a subject vomits after administration of study drug, the subject should be instructed not to retake the dose. Only if the subject vomits and the pills are visible, should the dose be retaken. Subjects should take the next scheduled dose. If vomiting persists, then the subject should contact the investigator.

5.8.6.2. Diarrhea

Diarrhea can be debilitating, and on rare occasions, it is potentially life-threatening. Based on experience with lapatinib alone or in combination with chemotherapy, diarrhea should be managed proactively to avoid complications or worsening of the subject's condition.

Experience thus far suggests that when lapatinib is combined with trastuzumab in the absence of concomitant chemotherapy, the rate and severity of diarrhea is similar to lapatinib as a monotherapy. Most diarrhea is uncomplicated CTC Grade 1 or 2. In rare cases, diarrhea can be debilitating, and potentially life-threatening with dehydration, renal insufficiency, and electrolyte imbalances.

Standardized guidelines for treating chemotherapy-induced diarrhea have been developed by an American Society of Clinical Oncology (ASCO) and were used to develop specific guidelines for lapatinib used as monotherapy or in combination with other treatments. Please refer to detailed guidelines which include definitions, management and study treatment holding and dose reduction rules in Appendix 7.

NOTE: if revisions are made between protocol amendments, the most updated version is included in SPM.

5.9. Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

5.9.1. Liver Chemistry Stopping and Follow-up Criteria

5.9.1.1. Liver Chemistry Stopping Criteria

All subjects who meet liver chemistry criteria requiring permanent discontinuation of study treatment must continue to be followed for the study assessments and procedures as defined in Section 7 and at the time points indicated in the Time and Events Schedule in Table 9

Liver chemistry stopping criteria 1-5 are defined as follows and are presented in a Figure in Appendix 4:

1. ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

   NOTE: If serum bilirubin fractionation is not immediately available, and if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 5xULN.
3. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥ 3xULN persists for ≥4 weeks
5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1 - 5 is met, do the following:

Immediately discontinue subject from study treatment

Report the event **within 24 hours** of learning its occurrence

Complete the liver event eCRF and SAE data collection tool if the event also meets the criteria for an SAE

All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, and if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury

Complete the liver imaging and/or liver biopsy CRFs if these tests are performed

Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below

- Withdraw the subject from the study after completion of the liver chemistry monitoring as described below (unless further safety follow-up is required or approval of drug restart is granted, as described in Section 5.9.2).
- Do not restart study treatment unless written approval for drug restart is granted (details for restarting study treatment are described in Section 5.9.2), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 5.9).

Subjects meeting criterion 5 should be monitored as frequently as possible.

In addition, for subjects meeting liver stopping criterion 1:

Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 5.9.1), and close monitoring

A specialist or hepatology consultation is recommended

Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For subjects meeting any of the liver stopping criteria 2 – 5:

Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section 5.9.1)

Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;

Subjects meeting criterion 5 should be monitored as frequently as possible.

5.9.1.2. Liver Chemistry Follow-up

For subjects meeting any of the liver chemistry stopping criteria 1 – 5, make every attempt to carry out the **liver event follow up assessments** described below:

Viral hepatitis serology including:

- Hepatitis A IgM antibody
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
- Hepatitis C RNA

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Hepatitis E IgM antibody.

Blood sample for pharmacokinetic (PK) analysis, obtained within [insert time interval recommended by clinical pharmacokinetics representative] of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

Fractionate bilirubin, if total bilirubin ≥2xULN.

Obtain complete blood count with differential to assess eosinophilia.

Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE form.

Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form.

Record alcohol use on the liver event alcohol intake form.

The following assessments are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).

Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**

Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed [Le Gal, 2005].

5.9.1.3. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the medical lead within 24 hours of learning of the abnormality to discuss subject safety
- Continue study treatment
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – X, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to Appendix 4 for algorithm of liver chemistry monitoring, interruption, stopping and follow up criteria.

5.9.2. Restarting Study Treatment

5.9.2.1. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval for drug restart can be considered where:

The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.

If the restart/rechallenge is approved in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The subject must also provide signed informed consent specifically for the study treatment (ST) restart/rechallenge. Documentation of informed consent must be recorded in the study chart.

Study drug must be administered at the dose specified.

Subjects approved for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

5.9.2.2. Drug Restart Following Transient Resolving Liver Events Not Related to Study Treatment

Approval for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified.
- Subjects approved for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

Refer to Appendix 5 for additional guidelines on liver safety drug restart and re-challenge.

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

The following will be recorded on the appropriate eCRF pages:

- A complete list of prescription and over-the-counter medications (including herbal medications) that have been taken **within two weeks** prior to the first dose of investigational therapy.

All treatments related to supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrhea medications, and analgesics, as appropriate.

All other concomitant medications (including over-the-counter medications) taken during the study.

NOTE: Lapatinib is likely to increase exposure to concomitantly administered drugs which are metabolized by CYP3A4 or CYP2C8. Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. **Caution** should be exercised

and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Refer to Table 8 for a list of CYP3A4 Inducers and Inhibitors that are prohibited from screening through discontinuation from lapatinib.

Concurrent treatment with bisphosphonates or denosumab is permitted. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis.

Questions regarding concomitant medications should be directed to the medical lead for clarification.

6.2. Prohibited Medications and Non-Drug Therapies

The following medications are prohibited from the specified time-point before the first dose of study treatment until withdrawal from study treatment (refer to Section 4.2 and Section 4.1):

Anticancer therapy should not be given until disease progression or withdrawal from study treatment. Subjects who receive concurrent anticancer therapy (i.e., cytotoxic or biologic) will not be allowed to continue study treatment;

Concurrent radiation therapy (radiotherapy will ONLY be allowed for palliation of pain for bone metastases and for spinal cord decompressions) and surgery for metastatic breast cancer, including resection of non-dominant metastases;

Hormonal therapy(ies), other than physiologic replacement;

Any other investigational drug (please refer to Section 4.1);

Because the composition, pharmacokinetics and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is strongly discouraged during the study;

Lapatinib is a substrate for CYP3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of lapatinib. The list of CYP3A4 inducers and inhibitors that are prohibited from screening through discontinuation from study is presented in Table 8. Therefore, caution should be used when lapatinib is used in conjunction with proton pump inhibitors as the concentration of lapatinib may be affected.

Table 8 CYP3A4 Inducers and Inhibitors

Drug Class	Specific Agents	Wash-out[1]
CYP3A4 Inducers		
rifamycin antibiotics	rifampicin, rifabutin, rifapentine	2 weeks
anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
antiretrovirals	efavirenz, nevirapine, tipranivir, etravirine	
glucocortical steroids (oral only)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)[2]	
other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
antibiotics	clarithromycin, erythromycin, troleandomycin, flucloxacillin	1 week
antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
antiretrovirals	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanavir	
calcium channel blockers	verapamil, diltiazem	
antidepressants	nefazodone, fluvoxamine	
gastrointestinal agents3	cimetidine	
fruit/fruit juices	grapefruit, star fruit, and papaw	
other	amiodarone	6 months
Miscellaneous		
antacids	Mylanta, Maalox, Tums, Rennies	1 hour before and after dosing
herbal supplements[4]	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	2 weeks

1. Time period between last dose of listed drug and first dose of lapatinib, required to avoid drug-drug interaction potential for toxicity (inhibitors) or loss of efficacy (inducers) that could make the subject unevaluable. Clinically appropriate substitution of drugs not on the list is recommended.
2. A standard 3-5 day course of dexamethasone at a dose following the institutions standard of care for the prevention and/or treatment of platinum-induced nausea and vomiting is allowed. Glucocortical steroid oral dose equivalents (in parentheses) to dexamethasone 1.5 mg (or less) given daily are allowed. Intravenous dosing should be considered if clinically appropriate.
3. Emetogenic chemotherapy may require 3-4 daily doses of aprepitant. CYP3A4 inhibition by oral (not IV) aprepitant may require a concurrent dose reduction of 1-2 lapatinib tablets.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact the medical lead or Clinical Scientist.

NOTE: If future changes are made to the list of prohibited medications, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter and revised version included in SPM.

6.3. Treatment after Discontinuation of Study Treatment or Withdrawal from/Completion of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition.

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) anticancer

therapy at the discretion of the treating physician. Every effort should be made to complete the end of study evaluations prior to initiating further anticancer therapy or dosing of an investigational agent (see Table 9).

For subjects who discontinue for any other reasons other than progression, new anti-cancer therapy will be recorded during the follow-up period until subject completion. New anticancer therapy should be documented on the eCRF with generic drug name, start and stop dates, regimen sequence, type of therapy, number of cycles/dose, dose units and reason for discontinuing post-study treatment.

6.4. Treatment of Study Treatment Overdose

There is no specific antidote for the inhibition of ErbB1 and/or ErbB2 tyrosine phosphorylation. The maximum oral doses of lapatinib that have been administered to date are 1800 mg once daily and 900 mg twice daily. Serum concentrations following 900 mg twice daily dosing are approximately twice that of 1800 mg once daily.

Subjects with suspected lapatinib overdose should be monitored until drug can no longer be detected systemically (at least 2.5 days). Follow-up physical examination with laboratory testing should be performed between 10 and 14 days after drug concentrations are undetectable and before the subject is discharged from the investigator's care.

For additional information, site pharmacist or authorized site personnel should refer to the lapatinib product characteristics for instruction [Lapatinib Summary of Product Characteristics, 2015].

If an overdose with trastuzumab should occur, the investigator, site pharmacist or authorized site personnel should refer to the trastuzumab product characteristics for instruction [Trastuzumab Summary of Product Characteristics, 2013].

Any SAEs that occur as a result of an overdose with the study treatment should be reported to the medical lead (see Section 7.4.5).

7. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments is outlined in Table 9.

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Refer to the Time and Events Table for the timing of all assessments (Table 9). Details on efficacy and safety assessments are presented in Section 7.3 and Section 7.4, respectively. Further details of study procedures and assessments can be found in the study procedures manual (SPM).

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

Table 9 Time and Events Table

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Procedures								
Informed Consent		X						
Inclusion / exclusion		X						
Demographics	Include birth year, race, ethnicity, and gender	X						
Surgical history		X						
Anti-cancer therapies		X[1]						X[14]
Past /current med conditions		X	X					
Translational Sample Collection								
Tumor Biopsy	[redacted] refer to Study Procedures Manual for biopsy sample collection, storage, and shipment	X					X[2]	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	procedures							
Archived/stored tumor tissue collection	Tumor tissue block or 15-20 unstained slides required	X						
[redacted]								
Efficacy Assessments								
Disease Assessment[3]	Target and nontarget lesions should be assessed using RECIST 1.1 within 28 days prior to randomization; assessments are conducted every 9 weeks until 54 weeks then every	X			X		X[4]	X[5]

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	24 weeks thereafter.							
Bone Scan[6]	Baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated. For subjects with bone disease at baseline, a bone scan is required every 18 weeks and at disease progression until Week 54 and then every 24 weeks or as clinically indicated	X						
Post study treatment efficacy for subjects who discontinued study treatment for reasons other than disease progression	Record dates of documented disease progression							X
Safety Assessments								
Concurrent meds		X	X	X			X	
Physical exam		X	X	X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Vital signs	Temperature, blood pressure and heart rate	X	X	X			X	
Weight & height	Height - screening only	X	X	X				
ECOG PS		X	X	X			X	
AE/toxicity	Subjects will be monitored every 6 weeks or at any contact with the subject during the study phases		X	X			X[7]	X[7]
ECHO or MUGA scan[8]	The same method of evaluation should be used for a subject throughout study duration	X				X	X	
12-lead ECG		X				X	X	
Laboratory Assessments[9]								
Hematology	Includes hemoglobin, hematocrit, red blood cell count, white blood cell count with absolute neutrophil count or differential, and platelet	X	X	X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	count							
Serum chemistry[10]	Includes sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin. magnesium	X	X	X			X	
Serum pregnancy test	Required for all women of childbearing potential; to be performed within 7 days prior to start of first dose of study treatment	X						

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Study Treatment Assessments								
Dispense lapatinib	A supply of lapatinib will be dispensed to subject with instructions for administration		X					
Trastuzumab administration	Weekly schedule is permitted in combination with chemotherapy. Window for dose administration is ± 3 days.		X	X				
Chemotherapy administration[11]	Dose and schedule as prescribed by the investigator		X					
Endocrine therapy with AI administration[12]	Dose and schedule as prescribed by the investigator in subjects with hormone receptor positive disease		X					
Study drug compliance	A record of the number of tablets dispensed to and returned by each subject must be maintained			X			X	

1. Prior therapies (screening visit only): include administration start and stop dates (month, year); date of radiographic confirmed progression.
2. Window for progression biopsy is +14 days from date of progression and prior to start of new anti-cancer therapy. Biopsy of metastatic tumor site only in subjects who discontinue study treatment due to disease progression.
3. Use the same method of measurement for target and nontarget lesions at all time points.
4. If the last radiographic assessment was obtained less than 9 weeks from study treatment discontinuation, radiographic assessments do not need to be repeated.
5. Subjects who discontinue study treatment for reasons other than progression (e.g. due to an AE) will have disease assessments done every 9 weeks until Week 54, then every 24 weeks thereafter until unequivocal progression, initiation of new anticancer therapy, death, withdrawal of consent, or end of study. At the end of study, if the last radiographic assessment was obtained less than 9 weeks earlier, radiographic assessment does not need to be repeated.
6. All bone scan abnormalities that may indicate metastases must be evaluated by X-ray (e.g., plain film), computed tomography (CT), or magnetic resonance imaging to confirm and/or quantify malignant lesions.
7. Safety monitoring will be performed until 30 days after the last dose for subjects who discontinued due to progression. Safety monitoring will continue for subjects who stopped study treatment for reasons other than disease progression until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first. Monitor all AEs/Serious AEs that are ongoing until resolution or stabilization of the event.
8. Additional ECHO/ MUGA scans should be performed when clinically indicated.
9. At the pre-dose assessment on Day 1, all laboratory results will be reviewed by the investigator. Any results outside of the normal range will be repeated (prior to the first dose) at the discretion of the investigator
10. Refer to Protocol Appendix 4 for further details
11. Chemotherapy will be administered throughout the study treatment phase based on the schedule chosen by investigator.
12. Endocrine therapy with AIs will be administered throughout the study treatment phase based on the schedule chosen by investigator.

[redacted]

For subjects who discontinue for any other reasons other than progression, new anti-cancer therapy will be recorded during the follow-up period until subject completion.Abbreviations: ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; MUGA, multigated acquisition scan.

7.1. Collection of Biopsies and Archival Tumor Tissue

Two biopsies will be collected for the study. In addition, archival/stored tumor tissue will be submitted to the central laboratory.

The first biopsy, referred to as the pre-treatment biopsy, will be taken at screening. This biopsy will be used to determine the breast molecular subtype of disease by central laboratory assessment. In addition, this biopsy will be used to centrally determine the HER2 and hormone receptor status of the tumor.

The second biopsy, referred to as the progression biopsy, will be taken at the time of radiologically determined disease progression. Additional details are provided in the SPM. The progression biopsy should be taken within 14 days of disease progression and prior to the start of any new anti-cancer therapy. The site of the biopsy at disease progression should be taken from the site biopsied at screening.

7.2. Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed at baseline.

7.2.1. Baseline Assessments

Baseline evaluations should be performed within 28 days prior to the first dose of study treatment, and include the following:

Demographic data: year of birth, race, ethnicity;

Vital signs: height, body weight, blood pressure, heart rate, temperature;

ECOG Performance Status (defined in Section 12.3 - Appendix 3: ECOG Performance Status);

Breast cancer history:

- Details of the primary tumor: estrogen and progesterone receptor status (performed by immunohistochemical methods), and HER2 status, including IHC and /or FISH/CISH/SISH analysis
- Clinical characteristics: date of diagnosis, stage and histology at initial diagnosis, date of documented diagnosis of metastatic disease by CT or MRI (if applicable), site(s) of metastases, line of therapy completed
- Prior treatment history: neoadjuvant, adjuvant and metastatic chemotherapy received (agent[s], date of last dose), biologic therapy, immunotherapy or hormonal therapy received
    - This includes the date of documented radiological disease progression during the most recent treatment

Document baseline CNS symptoms, if applicable.

7.2.2. Baseline documentation of target and non-target lesions

All baseline lesion assessments must be performed within 28 days prior to the first dose of study treatment.

Lymph nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

Pathological lymph nodes with < 15 mm and but ≥ 10 mm short axis are considered non measurable.

Pathological lymph nodes with ≥ 15 mm short axis are considered measurable and can be selected as target lesions; however lymph nodes should not be selected as target lesions when other suitable target lesions are available.

Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Biopsied lesions should not be used as target lesions.

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.3. Efficacy

Clinical endpoints regarding the assessment of tumor lesions must be performed using RECIST 1.1 [Eisenhauer, 2009].

7.3.1. Efficacy Endpoints

The primary efficacy endpoint of this study is the change in biomarkers associated with immunomodulation which is defined as change in expression levels of biomarkers as measured in tissue from the disease progression tumor biopsy, compared with expression levels as measured in the pre-treatment tumor biopsy.

The secondary efficacy endpoints of this study are:

Investigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months.

7.3.2. Clinical Efficacy Assessment

Disease progression and response evaluations will be determined according to the definitions established in RECIST 1.1 [Eisenhauer, 2009].

See the Time and Events Table (Table 9) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by any study treatment dose interruptions/delays. For post baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling.

The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled timepoint regardless of unscheduled assessments).

A baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g., presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required every 18 weeks until Week 54 and then every 24 weeks or as clinically indicated and at disease progression.In addition, in order to confirm a CR in a subject with bone disease at baseline, a bone scan must be performed 1 week prior to the first set of images showing CR to 4 weeks after the next protocol specified assessment.

For subjects without CNS disease at baseline, brain scans should only be performed as clinically indicated (e.g., symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required every 9 weeks until Week 54 and then every 24 weeks or as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the first set of images showing CR to 4 weeks after the next protocol specified assessment.

7.3.2.1. Assessment Guidelines

Please note the following:

The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion unless medically contraindicated.

All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.

Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.

Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.

If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/calipers to measure the size of the lesion, is required [Eisenhauer, 2009].

CT and MRI: <u>Contrast enhanced CT with 5 mm contiguous slices is recommended.</u> Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

7.3.2.2. Efficacy Assessment Schedule

Assessments within 4 Weeks Prior to First Dose

Clinical disease assessment for palpable or visual lesions;

Radiological disease assessments:

- CT or MRI scan of the chest, abdomen and pelvis
- Brain CT or MRI is required if previously documented brain metastases.
- Bone Scan (to include evaluation of skull, total spine, clavicle, ribs, pelvis, and long bones). All bone scan abnormalities at screening that could indicate metastases, must be evaluated by X-ray (e.g., plain film, CT, or MRI) to confirm and /or quantify malignant lesions;
- Documentation of tumor status at time of entry including all measurable disease and non-measurable disease.

7.3.2.3. Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Refer to Section 4.2 Permanent Discontinuation from Study Treatment and Time and Events Schedule (Table 9) for follow-up assessment of subjects who are to be followed up for disease progression after permanently discontinuing study treatment for any reasons other than disease progression.

Efficacy Assessments at Withdrawal (From Study and/or Study Treatment)

The following assessments will be performed, if possible, when a subject is withdrawn from study treatment and/or from study for any reason:

Radiographic disease assessments should be obtained at withdrawal for subjects who have not had documented progression at a previous timepoint. However, if the last radiographic assessment was obtained less than 9 weeks from withdrawal, radiographic assessments do not need to be repeated;

Efficacy Assessments for subjects who discontinued study treatment for reasons other than progression

Subjects who discontinue study treatment for reasons other than progression will have disease assessments done every 9 weeks until Week 54, then every 24 weeks thereafter until unequivocal progression, initiation of new anticancer therapy, death, withdrawal of consent or end of study (defined in section 10.5).

7.3.2.4. Assessment of Subject Completion

If the last radiographic assessment was more than 9 weeks prior to withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

7.3.3. Guidelines for Evaluation of Disease

Response to treatment will be determined for each evaluable subject according to definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009].with modification to allow a minimum lesion size of 10 mm with contiguous cuts of 5 mm or less.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes.) In the case of skin lesions, documentation by physical measurement using a ruler to estimate the size of the lesion is required. If skin lesions are being followed from baseline as target lesions, they must be evaluated at each time-point that requires tumor evaluations.

Conventional CT and MRI: Minimum sized lesion should be twice the reconstruction interval, with a minimum lesion size of 10 mm. The techniques should be performed with contiguous cuts of 5 mm or less in slice thickness. MRI is acceptable, but when used, lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Whenever possible, the same scanner should be used. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
Spiral CT: Minimum size of a baseline lesion may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. This specification applies to the tumors of the chest, abdomen, and pelvis.

Please note the following:

The same diagnostic method must be used throughout the study to evaluate a lesion unless medically contraindicated.

PET scans and ultrasound are not acceptable methods of disease assessment.

All measurements should be taken and recorded in millimetres (mm), using a ruler or calipers.

7.3.3.1. Measurable and Non-measurable Definitions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).

≥10 mm caliper/ruler measurement by clinical exam or medical photography.

≥20 mm by chest X-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

7.3.4. Response Criteria

7.3.4.1. Evaluation of Target Lesions

Definitions for assessment of response for target lesion(s) are as follows:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.

Not Applicable (NA): No target lesions at baseline.

Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.

If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

7.3.4.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).

Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

Not Applicable (NA): No non-target lesions at baseline.

Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g., non-target response does not have to be "Not Evaluable").

7.3.4.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

7.3.4.4. Evaluation of overall response

Table 10 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 10 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable			

Table 11 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for subjects with non-measurable only disease at baseline.

Table 11 Evaluation of Overall Response for Subjects with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=Not Evaluable		

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- 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) to confirm the CR.

7.3.4.5. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically based on the investigator's assessment of response at each time point.

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after randomization at a minimum interval of 56 days.

If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

7.4. Safety

7.4.1. Safety Endpoints

This study will describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy.

7.4.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 7.4.2.1 and Section 7.4.2.2.

7.4.2.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition

New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study

Signs, symptoms, or the clinical sequelae of a suspected interaction

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

“Lack of efficacy” or “failure of expected pharmacological action” *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from “lack of efficacy” will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

7.4.2.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

   NOTE: Death due to disease under study is to be recorded on the Death CRF form and does not need to be reported as an SAE.

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, 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.

g. Protocol-Specific SAEs:

   - All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35% direct) (or ALT ≥ 3x ULN and INR > 1.5, if INR measured) termed 'Hy's Law' events (INR measurement

is not required and the threshold value stated will not apply to patients receiving anticoagulants).

- NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2x ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations > 1.5 suggest severe liver injury
- Any new primary cancers

Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines. Interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1. As a precaution, the following will be reported as SAEs:

- Cardiac dysfunction will be reported as an SAE and will be defined as any sign(s) or symptom(s) of deterioration in left ventricular cardiac function that are Grade 3 (NCI CTCAE V 4.0) or a ≥ 20% decrease in left ventricular cardiac ejection fraction relative to baseline, which is below the institution's lower limit of normal. Refer to NCI CTCAE grading of left ventricular cardiac function. Also see Section 5.8.4 Criteria for Evaluating Cardiac and Respiratory Events.
- Any signs or symptoms of pneumonitis that are greater than Grade 3 (NCI CTCAE V 4.0) (defined as radiographic changes and requiring oxygen) dysfunction will be reported as an SAE. Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates.

Other hepatic events should be documented as an AE or an SAE as appropriate.

7.4.2.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and event felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as an SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

7.4.2.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

7.4.2.5. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

7.4.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the Death CRF form and does not need to be reported as SAE

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

7.4.3. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time a subject consents to participate in the study until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs (irrespective of causality) will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or study treatment must be recorded promptly to Novartis from the time a subject consents to participate in the study up to and including any follow-up contact, as indicated in section 7.4.5 and Table 12.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up.

7.4.4. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.5. Prompt Reporting of SAEs and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator as described in the following table once the investigator determines the event meets the protocol definition for that event.

Table 12 Time and Events

Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
CV events or death	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and bilirubin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

1. Liver chemistry elevations should be notified at onset to discuss subject safety.
2. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible
3. .INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Methods for, recording, evaluating, and following up on AEs and SAEs and procedures for completing and transmitting SAE reports are provided in the SPM. Procedures for post-study AEs and SAEs are provided in the SPM.

7.4.6. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met.

There is a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Notification will comply with country specific regulatory requirements relating to safety reporting to the regulatory authorityand investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.7. Pregnancy Testing, Prevention and Reporting

7.4.7.1. Pregnancy Test and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40 pg/mL (<140 pmol/L).

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test performed within 7 days prior to the first dose of study treatment. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below during the study until 30 days following the last dose of study treatment.

Novartis acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject’s entry and is the sole sexual partner for that female.

- Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 30 days after the last dose of study treatment.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).
- Implants of levonorgestrel where not contraindicated for this patient population or per local practice.
- Injectable progesterone where not contraindicated for this patient population or per local practice.
- Oral contraceptives (either combined or progesterone only) where not contraindicated for this patient population or per local practice.

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 30 days following the last dose of study treatment.

7.4.7.2. Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Novartis.

7.4.8. Laboratory Assessments

All protocol required laboratory assessments must be performed by a local lab.

Reference ranges for all safety parameters must be provided to Novartis and all laboratory results must be documented in the eCRF.

Prior to administration of the first dose of study drug, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range will be repeated (prior to the first dose) at the discretion of the investigator. Before the first dose of study drug, all laboratory results must be within the values outlined in Section 4.1.2. All laboratory tests with values that are significantly abnormal during participation in the study or within 5 days after the last dose of study drug should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Subjects will be required to have the laboratory assessments detailed in Table 13 (see Table 9 for specified study time-points).

Table 13 Laboratory Assessments

Hematology	**Standard Chemistry**[1]
Hemoglobin	sodium
Hematocrit	potassium
red blood cell count	calcium
Platelets	glucose
white blood cell count with differential	blood urea nitrogen (BUN) or urea
total neutrophils or Absolute Neutrophil Count (ANC)	creatinine[2]
	AST
Serum Pregnancy[3]	ALT
serum β-hCG	alkaline phosphatase
	total bilirubin[4]
	albumin
	magnesium

1. Chemistry evaluation of bicarbonate, chloride, and uric acid are not required
2. If serum creatinine is >1.2 mg/dL or 106 µmol/L, calculate creatinine clearance using standard Cockcroft and Gault method (refer to Section 12.9 Appendix 9)
3. Refer to Section 7.4.7 for further details on serum pregnancy testing.
4. Fractionated bilirubin (if testing is available) will also be assessed if total bilirubin ≥2 x ULN. See Section 5.9.1 Liver Chemistry Stopping and Follow-up Criteria

Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as clinically indicated.

7.6. Translational Research

Translational research will be performed on tissue and blood samples collected during the course of the trial to evaluate if immune markers are modulated by the treatment. These

analyses will highlight eventual changes in expression levels and/or presence (and localization) of immunological cells/markers in relation to treatment.

Analyses to identify biomarkers or profiles correlating with response, or disease characteristics that include but are not be limited to breast cancer histological grade and molecular subtype may also be performed if sample numbers allow.

All samples may be retained for a maximum of 15 years after the last subject completes the trial.

7.6.1. Tumor Biomarker Analysis

Markers of the immune microenvironment will be analyzed in pre-treatment tumor biopsies and in paired tumor tissue obtained at disease progression. These analyses will include tumor infiltrating lymphocytes (TILs) and a seleted immune mRNA gene expression panel (e.g. Nanostring platform), including mRNA markers for specific immune cell populations (e.g. CD8 positive T-cells, B-cells, Tregs). Gene expression levels in the disease progression biopsy will be compared to the baseline biopsy to assess how the treatments affect the immune response at the level of the tumor.

In addition, immunological cells (and protein markers) may be investigated; such analyses may include, but are not limited to PD-L1, CD8 protein expression levels as determinded by immunohistochemistry, Treg cells, macrophages, and expression of additional checkpoint molecules, in the context of tumor and tumor associated stroma.For the archival stored tissue, a formalin-fixed, paraffin-embedded tumor tissue block taken at a metastatic site or obtained at the time of original primary cancer diagnosis (biopsy or from definitive surgery) is required to be submitted to the central laboratory. Alternatively, sites may send 15-20 freshly sectioned, unstained slides containing 5-micron thick sections.

As image guidance has been shown to significantly increase the probability of success in obtaining core needle biopsies, it is therefore required for both percutaneous pre-treatment, and progression biopsies in this study.

Further details on sample collection, processing, storage and shipping procedures are provided in the SPM.

[redacted]

8. DATA MANAGEMENT

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives.

For this study subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to the sponsor (or designee) and be combined with data provided from other sources in a validated data system. The electronic data capture system InForm will be used to collect all of the subject information by the investigator.

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g. resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom drug dictionary. eCRFs (including queries and audit trails) will be retained by the sponsor, and copies will be sent to the investigator to maintain as the investigator copy.

9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

9.1. Hypotheses

The primary objective of this study is to determine if trastuzumab in combination with lapatinib or chemotherapy changes expression of biomarkers associated with immunomodulation. The primary endpoint will be analyzed by treatment arm with a descriptive intent only. The study is not powered to detect differences between the treatment arms and as such no formal treatment arm comparisons will be made.

9.2. Study Design Considerations

9.2.1. Sample Size Assumptions

This is a purely descriptive study. Due to difficulty in enrolling subjects into this trial, future enrolment was halted and the study will be terminated early.

A pre-treatment biopsy and a biopsy at disease progression will provide the samples for biomarker analysis.

9.2.2. Sample Size Sensitivity

Not applicable

9.2.3. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The Intent-to-Treat (ITT) Population will be used for the analysis of clinical efficacy and will consist of all subjects who were assigned to study treatment, regardless of whether they actually received study treatment.

The Evaluable Population (EP) will be used for the primary analysis of change in biomarkers at disease progression and will consist of all subjects who were assigned to study treatment and have both baseline and progression tumor biopsies available, with evaluable data for at least 1 biomarker.

The Safety Population will be used to assess clinical safety and tolerability and will consist of all subjects who were randomized and took at least 1 dose of study medication. This population will be based on the actual treatment received by the subjects.

9.3.2. Analysis Data Sets

The primary dataset for evaluation of changes in biomarker expression will be the Evaluable Population as defined in Section 9.3.1.

The primary dataset for assessing safety will be the Safety Population as defined in Section 9.3.1.

The primary dataset for assessing clinical efficacy endpoints will be the ITT Population as defined in Section 9.3.1. The Evaluable Population will be utilized to assess the relationship between on-treatment changes in biomarker expression and clinical endpoints.

9.3.3. Treatment Comparisons

9.3.3.1. Primary Comparisons of Interest

There will be no formal statistical comparisons between treatment arms in this study. All data presented including summary statistics are descriptive in nature.

The primary objective will be achieved by describing the change in biomarkers related to the specified mechanisms in the pre-treatment biopsy and the progression biopsy with each arm.

The data cut-off for the primary analysis will be defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier. Following the cut-off date for the primary analysis, the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study

- Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study
- At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit. Details on the handling of missing data are provided in Section 9.3.5.

9.3.4. Interim Analysis

No interim efficacy analyses are planned for this study.

9.3.5. Key Elements of Analysis Plan

Data will be listed and summarized according to the Novartis reporting standards, where applicable. Complete details will be documented in the reporting and analysis plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

For the analysis of PFS during study treatment period, if the subject received subsequent anticancer therapy prior to the date of documented progression or death, PFS will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

Details on the determination of tumor response are given in Section 7.3.4.

No adjustments for multiple comparisons will be made as there is no formal hypothesis testing.

Additional details on efficacy analyses are provided in Section 9.3.5.1. Similarly, additional details on safety analyses are provided in Section 9.3.5.2.

9.3.5.1. Efficacy Analyses

9.3.5.1.1. Primary Analysis

The primary biomarker endpoint is change in expression/percent presence levels of biomarkers as measured in tissue from the progression tumor biopsy, compared with expression/percent presence levels of these markers as measured in the screening tumor biopsy. Marker levels may be derived from measurements of mRNA or protein from biopsy samples.

The primary endpoint of changes in biomarker expression will be presented for each treatment arm for the evaluable population. Due to limited number of subjects enrolled as well as limited number of subjects with baseline biopsy and biopsy at disease progression, no formal statistical comparisons will be performed.

9.3.5.1.2. Secondary Analyses

This study is not powered to detect a clinically meaningful difference between the treatment groups in the secondary endpoints. Therefore, these analyses are considered exploratory and no formal hypothesis testing will be performed. Further details on these secondary endpoints will be documented in the RAP.

Overall Response Rate

ORR will be defined as the percentage of subjects achieving either a confirmed CR or PR tumor response at any time, according to the investigator assessment of response per RECIST 1.1 criteria. Subjects with unknown or missing response or who have withdrawn from the study will be included in the denominator as a nonresponder. Exact 95% CI for the tumor response rates in each arm will be calculated and the ITT Population will be used for the analysis.

Clinical Benefit Rate

CBR will be defined as the percentage of subjects achieving either a confirmed CR or PR tumor response at any time or maintaining SD for at least 24 weeks while on study, according to the investigator assessment of response per RECIST 1.1 criteria. Subjects with unknown or missing response or who have withdrawn from the study prior to completing 24 weeks of response assessments will be included in the denominator as a nonresponder. Exact 95% CI for the tumor response rates in each arm will be calculated and the ITT Population will be used for the analysis.

Progression-Free Survival

PFS will be defined as the interval of time between the date of randomization and the earlier of date of disease progression or date of death due to any cause. Disease progression will be based on the assessments by the investigator per RECIST 1.1 criteria. The date of documented disease progression will be defined as the date of radiological disease progression as assessed by the investigator based on imaging data, which will be the date of lesion evaluation. If a subject has neither progressed nor died, then PFS will be censored at the date of the last radiological scan assessed by the

investigator. Subjects who receive an alternative anticancer therapy will be censored at the initiation of the alternative therapy if scans or progression do not occur within a 14-day window as defined above. Additional details on censoring rules will be described in the RAP. PFS will be summarized using Kaplan-Meier curves. The Pike estimator [Berry, 1991] of the treatment HR based on the log-rank test will be provided, together with a 95% CI. The median PFS and first and third quartiles will be presented, along with 95% CI if there are sufficient numbers of progressions or deaths. These analyses will be done on the ITT population.

9.3.5.2. Safety Analyses

Safety endpoints are described in Section 2 and Section 7.4.

The Safety Population will be used for the analysis of safety data up to 30 days post-study treatment. Complete details of the safety analyses will be provided in the RAP.

Safety to be summarized to include at a minimum:

Exposure

Adverse events

Serious adverse events

Deaths

Adverse events leading to discontinuation of study treatment

Cardiotoxicity evaluations

Clinical laboratory evaluations

9.3.5.2.1. Extent of Exposure

The number of subjects administered study treatment will be summarized according to the duration of therapy.

9.3.5.2.2. Adverse Events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.0).

Events will be summarized by frequency and proportion of total subjects, system organ class, and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs, and AEs leading to discontinuation of study treatment.

If the AE is listed in the NCI-CTCAE (version 4.0) table, the maximum grade will be summarized.

Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AEs of special interest may be summarized separately: diarrhea, rash, LVEF, and liver toxicity.

The incidence of deaths and the primary cause of death will be summarized.

9.3.5.2.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI-CTCAE grade (version 4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI-CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which they were recorded (i.e., no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries, which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

9.3.5.2.4. Other Safety Measures

The results of scheduled assessments of vital signs, 12-lead ECG, ECHO (or MUGA scan), and ECOG performance status will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which they were recorded (i.e., no visit windows will be applied). All data will be listed. Further details will be provided in the RAP.

9.3.5.3. Translational Research Analyses

The results of translational research investigations will be reported in the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the RAP.

[redacted]

10. STUDY CONDUCT CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Novartis will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.

Subject informed consent.

Investigator reporting requirements.

Novartis will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Novartis procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

Data are authentic, accurate, and complete.

Safety and rights of subjects are being protected.

Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified

10.5. Study and Site Closure

The study will end when all subjects have completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression. All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal of consent or any other reasons mentioned in section 4.2.1.
In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study, no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subjects will be followed-up for safety and efficacy assessments (disease assessments done every 9 weeks until Week 54, then every 24 weeks) until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study

- Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study
- At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and Novartis Standard Operating Procedures.

Novartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Novartis determines that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**,Novartis will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

Novartis may close sites which fail to recruit within a predefined timeframe, as defined within the Study Procedures Manual.

10.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor

provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Novartis will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The sponsor aims to post a results summary to the Novartis Clinical Study Trial results website (www.novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of the study report, Novartis aims to submit results of the study for publication. When publication is not feasible, please refer to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results.A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Abraxane (nab paclitaxel) Product Information. January, 2005.

Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002; 2(2): 127-37.

Amin DN, Sergina N, Ahuja D, McMahon M, Blair JA, Wang D. Resiliency and vulnerability in the HER2-HER3 tumorigenic driver. Sci Transl Med. 2010; 2(16): 16ra7.

Arimidex (Anastrozole) Product Information. April, 2009.

Aromasin (Exemestane) Product Information. October, 2008.

Arteaga CL. Can trastuzumab be effective against tumors with low HER2/Neu (ErbB2) receptors? J Clin Oncol. 2006; 24(23): 3722-5.

Austin CD, De Mazière AM, Pisacane PI, et. al. Endocytosis and sorting of ErbB2 and the site of action of cancer therapeutics trastuzumab and geldanamycin. *Mol Biol Cell*. 2004; 15(12): 5268-82.

Baselga J, Albanell J, Molina MA, Arribas J. Mechanism of action of trastuzumab and scientific update. *Semin Oncol*. 2001; 28: 4-11.

Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, et. al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012c; 379: 633-40.

Baselga J, Carbonell, X, Castaneda-Soto, N-J et al. Phase II study of efficacy, safety and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Onco.l* 2005;.23(10): 2162-2171.

Baselga J, Cortes J, Im SA, Clark E, et. al. Biomarker analyses in CLEOPATRA: A phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC). *Cancer Res*. 2012a; 24: S5-1.

Baselga J, Cortes J, Kim SB, et.al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *New Eng J Med*. 2012b; 366: 109-119.

Benson A, Jaffer AA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Inducted Diarrhea. *J Clin Oncol.* 2004; 22:2918-2926.

Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. *Stat Med.* 1991; 10: 749-55.

Beslija S, Bonneterre J, Burstein H, et al. Second consensus on medical treatment of metastatic breast cancer. *Ann Oncol*. 2007; 18(2): 215-25.

Bianchini G, Pienkowski T, Im YH, et al (2016) Residual disease after HER2-directed therapies in the neosphere study: Modulation of tumor lymphocyte infiltration (TIL) and prognosis. J Clin Oncol 34 (suppl; abstr 517).

Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010; 28(7): 1124-30.

Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 study. *J Clin Oncol*. 2012; 30(21): 2585-92.

Blackwell KL, Pegram MD, Tan-Chiu E, et al. Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. *Ann Oncol*. 2009; 20(6): 1026-31.

Bruno R, Washington CB, Lu J-F, Lieberman B, Banken L, Klein P . Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol.* 2005; 56: 361-369.

Burstein HJ, Lieberman G, Slamon DJ, Winer EP, Klein P. Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy. *Annals of Oncol.* 2005; 16: 1772-1777.

Burstein HJ, Storniolo AM, Franco S, et al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol.* 2008; 19(6): 1068-74.

Cameron D, Casey M, Press M, et al. A Phase III Randomized Comparison of Lapatinib Plus Capecitabine Versus Capecitabine Alone in Women with Advanced Breast Cancer that Has Progressed on Trastuzumab: Updated Efficacy and Biomarker Analyses. *Breast Cancer Res Treat;* 2008; 112(3): 533-43.

Campone M, Berton-Rigaud D, Bourbouloux E, Sophie S, Zanetti A, Frenel JS. Her2 positive breast cancer: practices. *Bull Cancer*. 2011; 98(2): 154-63.

Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; on behalf of the ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012; 23 Suppl 7: vii11-9.

Carey LA, Berry DA, Ollila D, et al. Clinical and translational results of CALGB 40601: A neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer. J Clin Oncol 2013; 31(15 suppl): 500.

Chia SK, Speers CH, D'yachkova Y, et. al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007; 110: 973-9.

Cho HS, Mason K, Ramyar KX, et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature* 2003; 421(6924): 756-60.

Cobleigh M, Vogel C, Tripathy D, Robert et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999; 17: 2639-2648.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16: 31-41.

Cristofanilli M, Boussen H, Baselga J, et al. A Phase II combination study of lapatinib and paclitaxel as a neoadjuvant therapy in patients with newly diagnosed Inflammatory Breast Cancer (IBC). *Breast Can Res and Treat.* 2006; 100: 5S:Abstract:2.

Dave B, Migliaccio I, Gutierrez MC, et al. Loss of Phosphatase and Tensin Homolog or Phosphoinositol-3 Kinase Activation and Response to Trastuzumab or Lapatinib in Human Epidermal Growth Factor Receptor 2–Overexpressing Locally Advanced Breast Cancers *J Clin Oncol* 2011; 29(2): 166-73.

Denkert C, Loibl S, Noske A, et al (2010) Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol.;28(1):105-13.

Denkert C, von Minckwitz G, Brase JC, et al (2015) Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol.;33(9):983-91.

Di Leo A, Gomez HL, Aziz Z, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol.* 2008; 26(34): 5544-52.

Dieci MV, Bisagni G, Cagossi K, et al (2015) Tumor infiltrating lymphocytes and correlation with outcome in the Cher-LOB study. Cancer Res (9 Supplement) SABCS14-PD1-1, 1538-7445.

Dua R, Zhang J, Nhonthachit P, Penuel E, Petropoulos C, Parry G. EGFR over-expression and activation in high HER2, ER negative breast cancer cell line induces trastuzumab resistance *Breast Cancer Res Treat.* 2010; 122: 685-97.

Eisenhauer EA, Therasse P, Bogaerts J, et. al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45: 228-47.

Femara(Letrozole) Product Information. February, 2010.

Fisher B, Brown A, Mamounas E,, et al., Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997; 15(7): 2483-93.

Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. *Cancer*, 2002; 95(4): 681-95.

Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, Abdulkarim B. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. *J Clin Oncol.* 2006*;* 24: 5658-5663.

Garrett JT, Olivares MG, Rinehart C et al., Transcriptional and posttranslational up-regulation of HER3 compensates for inhibition of HER2 tyrosine kinase. *Proc Natl Acad Sci* 2011; 108: 5021-5026.

Garrett TP, McKern NM, Lou M, et al. The crystal structure of a truncated ErbB2 ectodomain reveals an active conformation, poised to interact with other ErbB receptors. *Mol Cell*. 2003; 11(2): 495-505.

Gemzar (gemcitabine) Product Information. May, 2007.

Geyer CE, Forster J, Lindquist L et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006; 355: 2733-2743.

Ghosh R, Narasanna A, Wang S, et al Trastuzumab Has Preferential Activity against Breast Cancers Driven by HER2 Homodimers. *Cancer Res* 2007; 71(5): 1.

Glück S, Ross JS, Royce M, McKenna EF Jr, Perou CM, Avisar E, Wu L. TP53 genomics predict higher clinical and pathologic tumor response in operable early-stage breast cancer treated with docetaxel-capecitabine ± trastuzumab. *Breast Cancer Res Treat*. 2012; 132: 781-91.

Gomez H, Chaves M, Doval D, Nag S, Chow L, Ang P, Ahmad N, Franco S, Berger M, Arbushites M, Westlund R, Zaks T, Stein S, Sledge G. Results from Phase II randomized study of lapatinib as first-line treatment for patients with HER2-amplified locally advanced or metastatic breast cancer. *SABC*, 2006, Abstract 1090.

Gomez Pardo P, Prat A, Bianchini G, Pickl M, Belousov A, et al. PAM50 intrinsic subtyping and pathologic responses to neoadjuvant trastuzumab-based chemotherapy in HER2-positive breast cancer. *J Clin Oncol*. 2011 29; 15_suppl: 554

Goss P, Smith I, O'Shaughnessy J, et al. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013 ; 14(1) :88-96.

Guarneri V, Frassoldati A, Bottini A, et al. Preoperative Chemotherapy Plus Trastuzumab, Lapatinib, or Both in Human Epidermal Growth Factor Receptor 2–Positive Operable Breast Cancer: Results of the Randomized Phase II CHER-LOB Study. *J Clin Oncol.* 2012; 30: 1989-1995.

Hannesdóttir L, Tymoszuk P, Parajuli N, et al (2013) Lapatinib and doxorubicin enhance the Stat1-dependent antitumor immune response. Eur J Immunol.;43(10):2718-29.

Hegde P, Rusnak D, Bertiaux M, et al. Delineation of molecular mechanisms of sensitivity to lapatinib in breast cancer cell lines using global gene expression profiles. *Mol Cancer Ther.* 2007; 6(5): 1629-40.

Herceptin (trastuzumab) Product Information. March, 2014.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Ignatiadis M, Singhal SK, Desmedt C, et al (2012) Gene modules and response to neoadjuvant chemotherapy in breast cancer subtypes: a pooled analysis. J Clin Oncol.;30(16):1996-2004.

Issa-Nummer Y, Darb-Esfahani S, Loibl S, et al (2013) Prospective validation of immunological infiltrate for prediction of response to neoadjuvant chemotherapy in HER2-negative breast cancer--a substudy of the neoadjuvant GeparQuinto trial. PLoS One.;8(12):e79775.

Jagiello-Gruszfeld A, Tjulandin Sergei S, Dobrovolskaya N, Manikhas A, Pienkowski T, Knott A, DeSilvio M, Oliva C. Lapatinib (L) with weekly paclitaxel (P) as first-line therapy for patients (pts) with HER2+ metastatic breast cancer (MBC). *Cancer Res.* 2009, 69: 3145.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006; 354(8): 809-20.

Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. *J Clin Oncol*. 2009; 27: 5538-5546.

Kallioniemi O, Holli K, Visakorpi T, Koivula T, Helin H, Isola J. Association of c-erB-2 protein overexpression with high rate of cell proliferation, increased risk of visceral metastasis and poor long term survival in breast cancer. *Int J Cancer* 1991, 49 (5): 650-5.

Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study. *J Clin Oncol.* 2009; 27(33): 5529-37.

Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res*. 2006; 66(3): 1630-9.

Lapatinib Summary of Product Characteristics. Novartis Europharm Limited, UK. 11 August 2015.

Laoui D, Van Overmeire E, Van Ginderachter JA. (2013) Unsuspected allies: chemotherapy teams up with immunity to fight cancer. Eur J Immunol.;43(10):2538-42.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Leyland-Jones B, Gelmon K, Ayoub J-P, et al: Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. *J Clin Oncol.* 21: 3965-3971, 2003.

Lonning PE. Clinical Pharmacokinetics of Aromatase Inhibitors and Inactivators. *Clin Pharmacokinet.* 2003; 42(7): 619-631.

LoRusso PM, Jones SF, Koch KM, et al.. Phase I and pharmacokinetic study of lapatinib and docetaxel in patients with advanced cancer. *J Clin Oncol.* 2008; 26(18): 3051-56.

Loi S, Sirtaine N, Piette F, et al. (2013) Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol.;31(7):860-7.

Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, Kellokumpu-Lehtinen PL, Bono P, Kataja V, Desmedt C, Piccart MJ, Loibl S, Denkert C, Smyth MJ, Joensuu H, Sotiriou C (2014) Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544-50.

Maruyama T, Mimura K, Izawa S, et al. Lapatinib enhances herceptin-mediated antibody-dependent cellular cytotoxicity by up-regulation of cell surface HER2 expression. *Anticancer Res.* 2011 ; 31(9): 2999-3005.

Meric F, Hung MC, Hortobagyi GN, Hung KK. HER-2/neu in the management of invasive breast cancer. J Am Coll Surg. 2002; 194(4): 488-501.

Micheli A, Mugno E, Krogh V, Quinn MJ, Coleman M, Hakulinen T, Gatta G, Berrino F, Capocaccia R. EUROPREVAL Working Group. Cancer prevalence in European registry areas. *Ann Oncol*. 2002; 13(6): 840-65.

Montemurro M, Prat A, Rossi V, et al. Potential biomarkers of long-term benefit from single-agent trastuzumab or lapatinib in HER2-positive metastatic breast cancer. *Mol* Oncol. 2013; 8(1): 20-6.

Navelbine (vinorelbine tartrate) Product Information. Jan, 2002.

NCCN. Clinical Practice Guidelines in Oncology, V.1.2011 (dated 11/08/2010) from http://www.nccn.org

NCI. National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. *NIH publication # 09-7473.* 2009.

Nicholson RI, McClelland RA, Robertson JF, Gee JM. Involvement of steroid hormone and growth factor cross-talk in endocrine response in breast cancer. *Endocr Relat Cancer* 1999; 6: 373–87.

O'Brien NA, Browne BC, Chow L, et al Activated phosphoinositide 3-kinase/AKT signaling confers resistance to trastuzumab but not lapatinib. *Mol Cancer Ther.* 2010; 9 1489-1502.

O'Donovan N, Byrne AT, O'Connor AE, et al. Synergistic interaction between trastuzumab and EGFR/HER-2 tyrosine kinase inhibitors in HER-2 positive breast cancer cells. *Invest New Drugs.* 2011; 29(5): 752-9.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5: 649-655.

Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J*. 2000; 19(13): 3159-67.

Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol*. 2009; 27: 1160–1167.

Pegram M, Liao J. Trastuzumab treatment in multiple lines: Current data and future directions. *Clin Breast Cancer*. 2012; 12(1): 10-18.

Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. *Clin Breast Cancer* 2005; 6(5):425-32.

Perou C, Surlie T, Eisen M, et al. Molecular portraits of human breast tumors. *Nature* 2000; 406: 747-752.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al: Trastuzumab after adjuvant chemotherapy in HER2-positive Breast Cancer. *N Engl J Med.* 2005; 353(16): 1659 - 1672.

Pivot X, Semiglazov V, Żurawski B, et al. CEREBEL (EGF111438) An open label randomized phase III study comparing the incidence of CNS metastases in patients (pts) with HER2+ Metastatic Breast Cancer (MBC), treated with Lapatinib plus Capecitabine (LC) versus Trastuzumab plus Capecitabine (TC) ESMO 2012. Annual Meeting: LBA11. 2012.

Prat A, Bianchini G, Thomas M, et al. Research-Based PAM50 Subtype Predictor Identifies Higher Responses and Improved Survival Outcomes in HER2-Positive Breast Cancer in the NOAH Study. *Clin Cancer Res.* 2014; 20(2):511-21.

Rebucci M, Michiels C. Molecular aspects of cancer cell resistance to chemotherapy. *Biochem Pharmacol*. 2013; 85: 1219-26.

Rezai K, Urien S, Isambert N, et al. Pharmacokinetic evaluation of the vinorelbine-lapatinib combination in the treatment of breast cancer patients. *Cancer Chemother Pharmacol*. 2011; 68(6): 1529-36.

Rimawi M, Weiss H, Arpino G, et al. Potent inhibition of ErbB1(EGFR) /ErbB2(HER2) Erb(HER) pathway with estrogen deprivation is a superior therapeutic strategy in ER-positive HER2-neu overexpressing breast tumor xenografts. *Breast Cancer Res Treat*. 2006; 100: S28 Abstract 302.

Rimawi MF, Wiechmann LS, Wang YC, et al. Reduced dose and intermittent treatment with lapatinib and trastuzumab for potent blockade of the HER pathway in HER2/neu-overexpressing breast tumor xenografts. *Clin Cancer Res.* 2011; 17(6): 1351-61.

Ring A, Dowsett M. Human epidermal growth factor receptor-2 and hormonal therapies: clinical implications. *Clin Breast Cancer*. 2003, 4: S34-41

Ritter CA, Perez-torris M, Rinehart et al,Human breast cancer cells selected for resistance to trastuzumab in vivo overexpress epidermal growth factor receptor and ErbB ligands and remain dependent on the ErbB receptor network *Clin Cancer Res* 2007; 13: 4909-19

Robidoux A, Tang G, Rastogi P, Geyer CE, Azar CA, Atkins JN, et al. Evaluation of lapatinib as a component of neo-adjuvant therapy for HER2+ operable breast cancer: NSABP protocol B-41. *J Clin Oncol*. 30, 2012 (suppl; abstr LBA506).

Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer *N Engl J Med.* 2005; 353: 1673-1684.

Rusnak DW, Lackey K, Affleck K, et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human and tumor-derived cell lines in vitro and in vivo. *Mol Cancer Ther.* 2001; 1(2): 85-94.

Sánchez-Martín M, Pandiella A. Differential action of small molecule HER kinase inhibitors on receptor heterodimerization: therapeutic implications. *Int J Cancer*. 2012; 131(1): 244-52.

Sauter G, Lee J, Bartlett JM, Slamon DJ, Press MF. Guidelines for human epidermal growth factor receptor 2 testing: biologic and methodologic considerations. *J Clin Oncol.* 2009; 27: 1323-33.

Scaltriti M, Rojo F, Ocaña A, Anido J, Guzman M, Cortes J, et. al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. *J Natl Cancer Inst*. 2007; 99(8): 628-38.

Scaltriti M, Verma C, Guzman M, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. *Oncogene*. 2009; 28(6): 803-14.

Seidman A, Hudis C, Pierri M, Shak S, Paton V, Ashby M, Murphy M, Stewart S, Keefe D. Cardiac dysfunction in the trastuzumab clinical trial experience. *J Clin Oncol.* 2002; 20(5): 1215-21.

Slamon D, Clark G, Wong S, Levin W, Ullrich A, McGuire W. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987*;* 235: 177-82.

Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Eng J Med.* 2011; 365(14): 1273-83.

Slamon DJ, Godolphin W, Jones LA, et. al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; 244: 707-12.

Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A et al. Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med.* 2001; 344(11): 783-792.

Sliwkowski MX, Lofgren JA, Lewis GD, Hotaling TE, Fendly BM, Fox JA. Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). *Semin Oncol*. 1999, 26: 60-70.

Smith I, Marion P, Gelber R, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2 positive breast cancer: a randomized controlled trial. *Lancet* 2007; 369: 29-36.

Sobottka B, Pestalozzi B, Fink D, et al (2016) Similar lymphocytic infiltration pattern in primary breast cancer and their corresponding distant metastases. Oncoimmunology. 5;5(6):e1153208.

Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98: 10869–10874.

Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2013; 14(6): 461-71.

Tan M, Yu D. Molecular mechanisms of ErbB2-mediated breast cancer chemoresistance. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000. Available from: http://www.ncbi.nlm.nih.gov/books/NBK6194/.

Taxol (paclitaxel) Product Information. July, 2000.

Taxotere (docetaxel) Product Information. May, 2004.

The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. *Nature.* 2012; 490(7418): 61-70.

Trastuzumab Summary of Product Characteristics, Roche Registration Ltd, UK 26 Feb 2013.

Tripathy D, Slamon DJ, Cobleigh M, et al. Safety of Treatment of Metastatic Breast Cancer With Trastuzumab Beyond Disease Progression. *J Clin Onc*ol. 2004; 22: 1063-1070

TYVERB (lapatinib) Package Leaflet. Novartis Europharm Limited, UK. 11 August 2015.

Urruticoechea A, Rizwanullah M, Im SA, et al (2016) PHEREXA: A phase III study of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. J Clin Oncol 34, 2016 (suppl; abstr 504)

Verma S, Miles D, Gianni L, Krop IE, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012; 367(19): 1783-91.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002; 20: 719-26.

von Minckwitz G, Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study. *J Clin Oncol.* 2009; 27: 1999-2006.

Wang YC. Different mechanisms for resistance to trastuzumab versus lapatinib in HER2-positive breast cancers - role of estrogen receptor and HER2 reactivation. *Breast Cancer Res.* 2011; 13: R121.

Wildiers H, Kim SB, Gonzalez-Martin A, LoRusso PM, et al. T-DM1 for HER2-positive metastatic breast cancer (MBC): Primary results from TH3RESA, a phase 3 study of T-DM1 vs treatment of physician's choice. European Society for Medical Oncology (EMSO) 17th European Cancer Congress (ECCO), 2013, Ansterdam, Netherlands.

Wolchok JD, Hoos A, O'Day S, Weber JS. Guidelines for evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009; 15(23): 7412-20.

Wong H, Leung, R, Kwong, A et al. Integrating Molecular Mechanisms and Clinical Evidence in the Management of Trastuzumab Resistant or Refractory HER-2 Metastatic Breast Cancer The Oncologist 2011; 16: 1535–1546.

Wood ER, Truesdale AT, McDonald OB, Yuan D, Hassell A, Dickerson S, et al. A Unique Structure for Epidermal Growth Factor Receptor Bound to GW572016 (Lapatinib): Relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. Cancer Res. 2004; 64(18): 6652-6659.

Xeloda (capecitabine) Product Information. April, 2006.

Xia W, Gerard CM, Liu L, et al. Combining lapatinib (GW572016), a small molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, with therapeutic anti-ErbB2 antibodies enhances apoptosis of ErbB2-overexpressing breast cancer cells. *Oncogene.* 2005; 24(41): 6213-21.

Xia W, Liu LH, Ho P et al. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. *Oncogene* 2004; 23: 646–653.

Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. *Nat Rev Cancer*. 2012; 12(8): 553-63.

12. APPENDICES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.2. Appendix 2: Country Specific Requirements

No country-specific requirements exist.

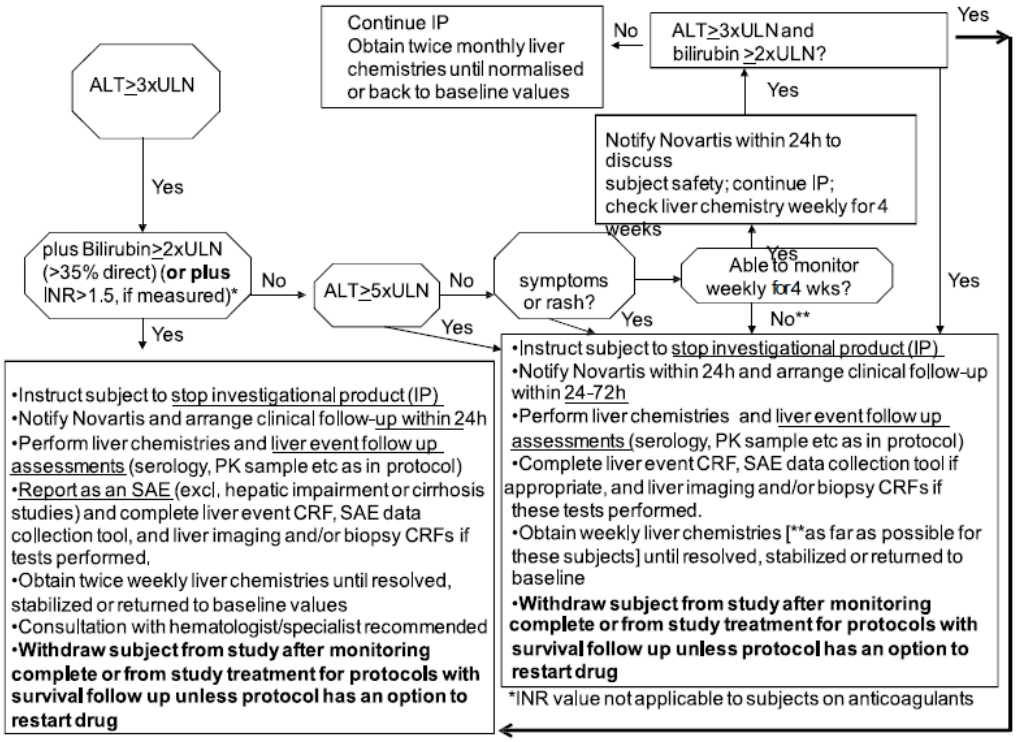
12.3. Appendix 3: ECOG Performance Status

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

1. As published in [Oken, 1982]

12.4. Appendix 4: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Liver Safety Algorithm



IP may be re-challenged if protocol provides this option in Section 5.9.2.

12.5. Appendix 5: Liver Safety Drug Restart or Rechallenge Guidelines

1. Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternative medicine available.
2. Drug restart may be considered for liver safety events with a clear underlying cause (e.g., biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis, or hypersensitivity (fever, rash or eosinophilia) and drug not associated with HLA genetic marker of liver injury) when liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3 x ULN.

Liver Events Possibly Related to IP - Drug Restart/Rechallenge Following Possible Drug-induced Liver Injury Challenge Guidelines

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g., fever, rash, eosinophilia), jaundice or bilirubin ≥2 x ULN or INR >1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3]

Decision Process for Drug Restart Approval or Disapproval (also see *Figure 2*)

Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment

Medical lead & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist (Table 14)

Table 14 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of the study treatment (ST) for this subject and no alternative therapy. **Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin≥2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**:		
• IP associated with known preclinical hepatic liability/ injury		

Principal Investigator (PI) Actions:

The PI must obtain Ethics Committee or Institutional Review Board review of drug reinitiation, as required.

PI must discuss the possible benefits and risks of drug reinitiation with the subject.

The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.

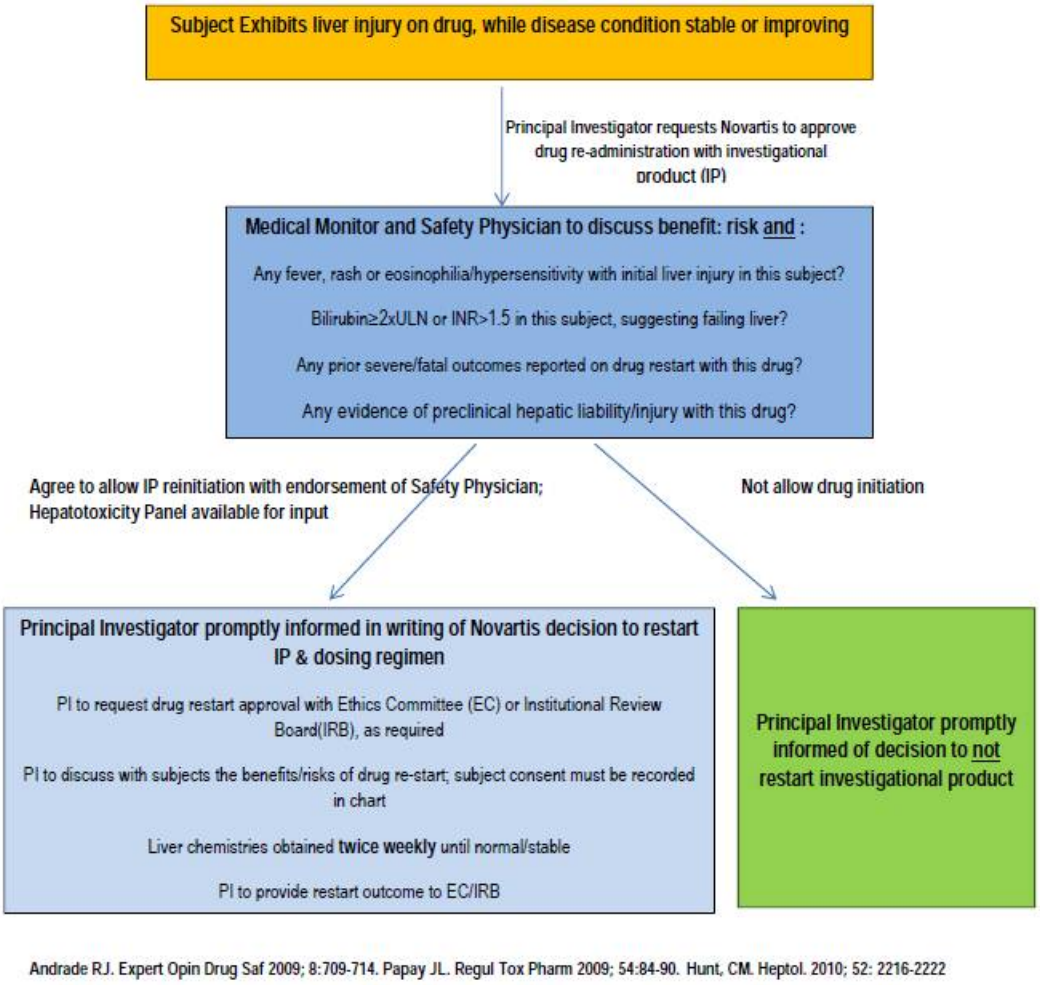
The drug must be reinitiated at Novartis approved dose(s).

Liver chemistries should be followed twice weekly until stable.

The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.

Notification of any adverse events, as per Section 7.4.2 - Section 7.4.6.

Figure 2 Process for drug restat after possible drug-induced liver injury



Andrade RJ. Expert Opin Drug Saf 2009; 8:709-714. Papay JL. Regul Tox Pharm 2009; 54:84-90. Hunt, CM. Heptol. 2010; 52: 2216-2222

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

Drug Restart Guidelines

Novartis Decision Process for Drug Restart Approval or Disapproval (also see Figure 3)

Principal Investigator (PI) requests consideration of drug reinitiation for a subject stable or improving on study treatment (ST), who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and resolves.

Medical lead & Clinical Safety Physician to review the subject's diagnosis, restart risk factors & complete checklist (Table 15).

Table 15 Checklist for Phase III drug restart after well-explained liver injury (e.g., biliary, pancreatic, hypotensive events, CHF, acute viral hepatitis), liver chemistries improving to normal or ≤1.5 x baseline and ALT <3 x ULN.

	Yes	**No**
Is subject stable or improving on the study treatment (ST)?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST≥ALT, typically <10xULN)		
• IP associated with liver injury and an HLA genetic marker (e.g., lapatinib, abacavir, amoxicillin/clavulanate)		

Principal Investigator (PI) Actions

The PI must obtain Ethics Comm. or Institutional Review Board review of drug reinitiation, as required.

PI must discuss the benefits and risks of drug reinitiation with the subject.

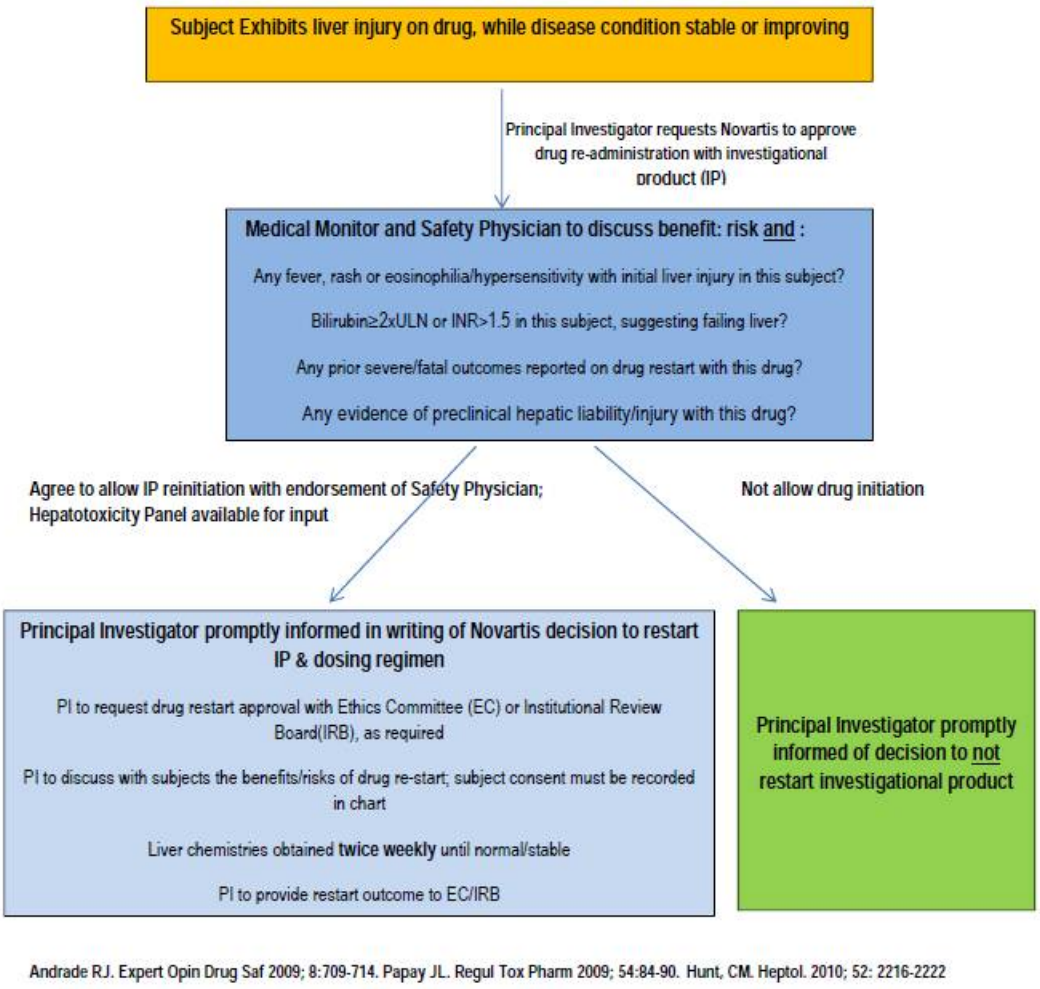
The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.

Liver chemistries should be followed weekly until stable.

The Ethics Committee or Institutional Review Board must be informed of the patient's outcome, as required.

Notification of any adverse or serious adverse events, as per Section 7.4.2 - Section 7.4.7.

Figure 3 Process for drug restart approvals



Andrade RJ. Expert Opin Drug Saf 2009; 8:709-714. Papay JL. Regul Tox Pharm 2009; 54:84-90. Hunt, CM. Heptol. 2010; 52: 2216-2222

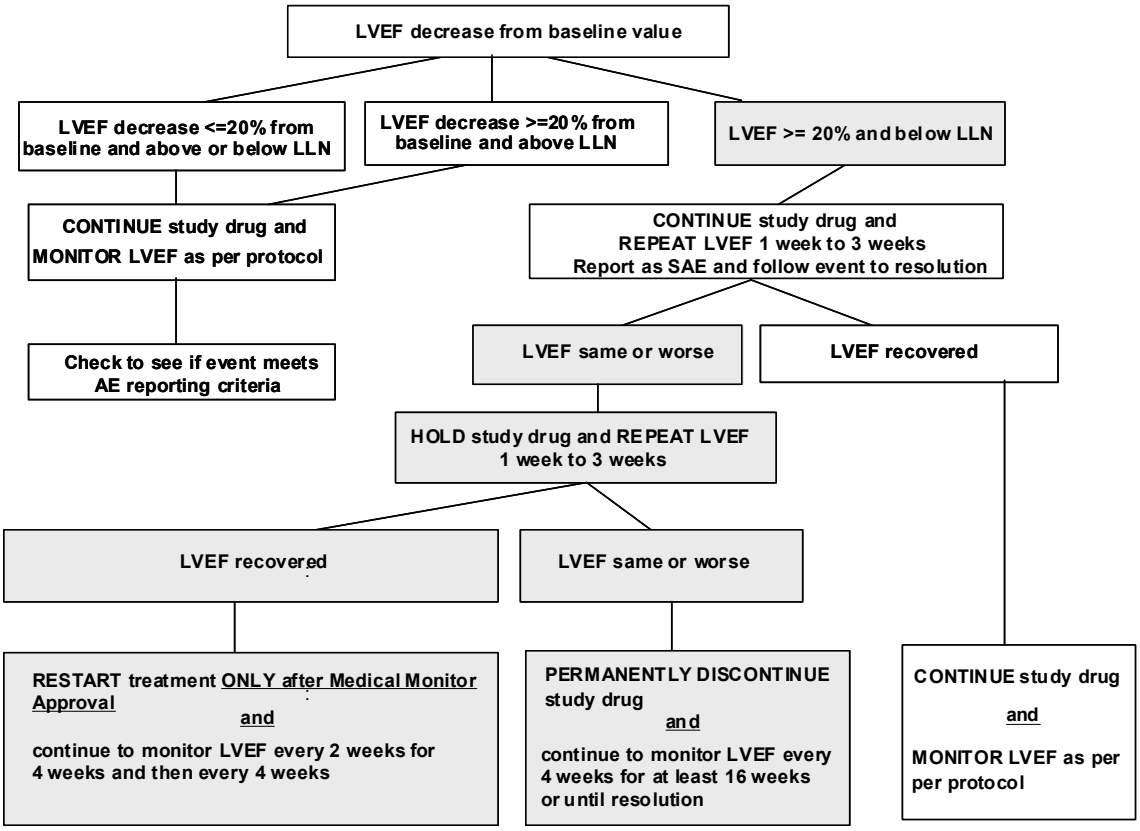
References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

12.6. Appendix 6: Asymptomatic Cardiac Event Assessment



12.7. Appendix 7: Diarrhea Mangement Guidelines

Background

Experience thus far suggests that when lapatinib is used as monotherapy 51% of patients experience diarrhea; most diarrhea presents as uncomplicated NCI CTCAE Grade 1 or 2 (G1 30%, G2 15%, G3 6%, G4<1%) (Crown, 2008).

In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea (Benson, 2004). Presented in the sections below are the recommended guidelines for the management of diarrhea in subjects receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel (Benson, 2004).

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If subjects present with diarrhea of any Grade, check they are taking lapatinib correctly, i.e., single daily dose, rather than splitting it through the day. Obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the lapatinib treatment period.

Definitions

National Cancer Institute (NCI) guidelines define diarrhea compared with baseline (Table 16).

Table 16 NCI Common Terminology Criteria for Grading Diarrhea Adverse Events1

Adverse Event Grade	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared with baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared with baseline;
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Uncomplicated diarrhea is considered mild-to-moderate and defined as CTCAE Grade 1 or 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as any CTCAE Grade 3 or 4 diarrhea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping
- Nausea/vomiting ≥Grade2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

Management Guidelines for Subjects Receiving Lapatinib Alone or as Combination Therapy

A) Uncomplicated Diarrhea

I. CTCAE Grade 1

NOTE: Subject should be instructed to: start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and call their physician.

1. Administer loperamide*
   a. Initial dose 4 mg followed by 2 mg after every unformed stool. Re-evaluate after 24 hours, if:
      i. Diarrhea is resolving:

- Continue loperamide treatment at 2 mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
    - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns

ii. Diarrhea is not resolving:

- Administer loperamide at 2 mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours. If diarrhea is resolving, administer loperamide at 2 mg after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhea is not resolving continue loperamide treatment at 2 mg every 4 hours and re-evaluate every 24 hours.

b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium).

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
    a. Stop all lactose containing products and eat small meals
    b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
        - Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
    c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
    d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
        - Avoid acidic drinks such as tomato juice and fizzy soft drinks
    e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots) , evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment.

If Grade 1 diarrhea persists for ≥2 weeks, refer to the management guidelines for Persistent Grade 2 Diarrhea.

II. CTCAE Grade 2

NOTE: Subject should be instructed to call physician at first episode of diarrhea and start supportive care immediately

1. Administer loperamide*
   a. Initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
      i. Diarrhea is resolving, continue loperamide treatment at 2 mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving, consider loperamide dose of 2 mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (i.e.,octreotide, budesonide or tincture of opium).
         - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
      - Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      - Avoid acidic drinks such as tomato juice and fizzy soft drinks
   e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet. Refer to Section IV "Recurrent Diarrhea" for study treatment guidelines.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

III. Persistent (≥ 3days/72 hours) Grade 2 Diarrhea: hold lapatinib and chemotherapy (if applicable) until diarrhea resolves (<Grade 1/return to baseline bowel pattern).

1. If supportive care measures and the interruption of study treatment (i.e., lapatinib and if applicable chemotherapy) are ineffective in treating persistent Grade 1 or Grade 2 diarrhea, perform stool work-up, CBC, electrolytes and other tests as appropriate, consider consulting with a gastrointestinal (GI) specialist.
   a. After diarrhea resolves (<Grade 1/return to baseline bowel pattern), resume treatment with lapatinib and chemotherapy (if applicable).

IV. Recurrent Diarrhea (more than 1 occurrence of Grade 2 diarrhea): once the second occurrence of Grade 2 diarrhea resolves to ≤Grade 1, consider reducing the dose of lapatinib by 250 mg or 1 tablet, unless the lapatinib dose already had been reduced to 750 mg. No further dose reduction is recommended for subjects taking lapatinib at 750mg.

1. Consider a dose reduction for chemotherapy (if applicable)

B) Complicated Diarrhea

I. CTCAE Grade 3 or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration)

1. Subject **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool*****
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia

Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤Grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750mg, contact *medical lead for further guidance*):

a. Consider a dose reduction for chemotherapy (if applicable)

7. Supportive care and other interventions should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
8. Intervention may require hospitalization for subjects most at risk for life threatening complications

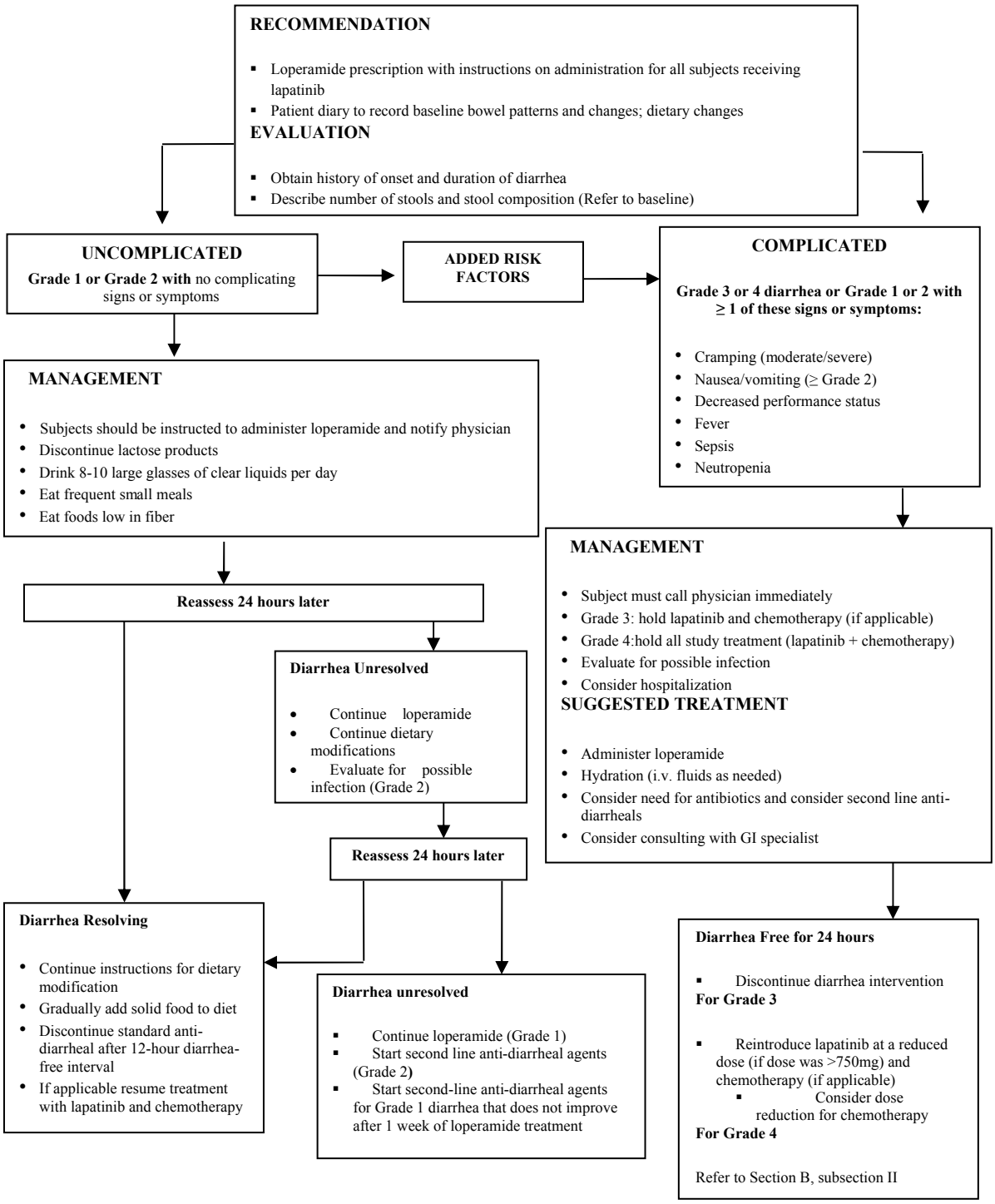
II. CTCAE Grade 4

1. Subject must call physician immediately for any Grade 4 diarrhea event
2. Hold treatment with lapatinib, hold chemotherapy or other concurrent anticancer therapy (if applicable)
   - Contact the medical lead to discuss the patient case history and the possibility of re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤Grade 1)
     (***INFO: NOTE****: Can Modify* Figure 4 *Grade 4 with this guidance; For Investigator sponsored studies substitute the above recommendation with the following:* Evaluate the patient case history when deciding on the re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤Grade 1)
3. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool*****
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Recommend consulting with GI specialist
7. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
8. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

*****It is recommended that the maximum cumulative daily dose of loperamide follows local guidance

Refer to and follow the recommended supportive care guidelines in the previous sections and as depicted in Figure 4.

Figure 4 Algorithm for the management of diarrhea in subjects treated with lapatinib-based therapy



1. For Grade 1 diarrhea that persists for 2 weeks or longer, refer to Section III
2. For Grade 2 diarrhea that persists longer than 3 days/72 hours, refer to Uncomplicated Diarrhea Section III
3. For recurrent diarrhea, refer to Uncomplicated Diarrhea Section IV for further management guidelines

References

American Cancer Society. Coping with physical and emotional changes: Diarrhea: what the subject can do.
Diahttp://www.cancer.org/docroot/MBC/content/MBC_2_3X_Diarrhea.asp

Benson A, Jaffer AA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Inducted Diarrhea. Journal of Clinical Oncology 2004; 22:2918-2926.

Crown JP, Burstein HA, Boyle F, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. Breast Cancer Res Treat 2008; 112:317-325.

12.8. Appendix 8: Dermatological Assessment

Dermatological Monitoring

As part of their physical exam, subjects must have a thorough skin exam prior to the Day 1 of study therapy or randomization. The exam should include the scalp, previously radiated areas, hair, and nails. In addition, if clinically indicated an examination of the oral/genital mucosa should be done.

Subsequent dermatological evaluations must be performed at every study visit unless a dermatological AE has developed, in which case a more frequent surveillance is warranted until the event resolves.

In addition, any subject who develops signs and symptoms of dermatological disease (pruritus, tenderness, visible skin or nail lesions) should undergo a full body skin exam.

12.8.1. Purpose of Dermatological Monitoring

- To facilitate dermatological safety throughout the trial in all subjects by applying an algorithm for the discontinuation of lapatinib or its combination.
- To assess whether a holding/stopping rule imposed during the course of treatment leads to excessive dermatological toxicity.
- To identify the incidence of dermatological adverse events (AEs) for lapatinib, or the combination of lapatinib with other agents by defining pre-specified dermatological toxicity.

12.8.2. Evaluation and Grading Guide

12.8.2.1. The Most Commonly Reported Dermatological Reactions

- Papulopustular rash affecting especially the upper body, including face and scalp. Association with pruritus, burning or tenderness may occur;
- Maculopapular rash affecting the upper body. Pruritus may also occur;
- Nail or hair changes – any hair changes or loss, or paronychia;
- Dry skin, pruritus, and photosensitivity (Table 17).

Table 17 NCI-CTCAE Dermatological Reactions (version 4.0)

Adverse Event (Short name)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash maculo-papular	Macules/papules covering <10% body surface area (BSA) with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Rash: Acne/acneiform (Acne)	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Nail Loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-

Adverse Event (Short name)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Pruritus/itching (Pruritus)	Mild or localized; topical intervention indicated	IIntense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	
Dry skin (Dry skin)	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	
Alopecia	Hair loss of up to 50% of normal for that individual that is not obvious	Hair loss of >50% normal for that individual that is readily apparent to	-	-	

Adverse Event (Short name)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact			
Photosensitivity (Photosensitivity)	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death

12.8.3. Severe Skin Events

- Lapatinib-related severe dermatological events are infrequent (1-3%). Table 17 displays the NCI-CTCAE (version 4.0) ≥ Grade 3 skin events, which are defined as:Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL
- Surgical intervention or IV antibiotics indicated; limiting self care ADL
- Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated
- Covering >30% BSA and associated with pruritus; limiting self care ADL
- Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs

Despite the rarity of these events among subjects treated with lapatinib, it is recommended that subjects which present with these events be assessed for shortness of breath, angioedema, or generalized mucosal/cutaneous affectation with blisters or ulcers, suggestive of Type I hypersensitivity and/or NCI-CTCAE Grade 4 rash or dermatologic event, manifested as toxic epidermal necrolysis (i.e., Stevens-Johnson's Syndrome etc). If Grade 4 rash or dermatologic event occurs, lapatinib must be permanently discontinued.

12.8.4. Stopping and holding rules

If any Grade 4 dermatologic event occurs, lapatinib must be permanently discontinued.

12.8.4.1. Holding rule

For NCI-CTCAE Grade 3 dermatological reactions, or a Grade 2 dermatological reaction which is not improved after 2 weeks with recommended management strategies, a brief (up to 14 days) therapy interruption is recommended; the daily dose of lapatinib should then be reinstated. In some cases, the skin event may improve without the need for interrupting therapy with lapatinib. In the lapatinib clinical program to date, many subjects were able to resume lapatinib therapy at the same dose after resolution of skin event; these subjects had less extensive and/or severe skin events.

12.8.4.2. Re-challenge

One re-challenge may be considered, if indicated in the opinion of the investigator, for subjects who present with NCI-CTCAE Grade 3 skin events which recover briskly to NCI-CTCAE Grade 1 (within 14 days) after holding lapatinib.

12.8.4.3. Stopping rules

Lapatinib should be permanently discontinued if an NCI-CTCAE Grade 3 dermatological reaction is intolerable to the subject despite recommended treatment interventions, or if a Grade 3 reaction recurs after one drug interruption/re-challenge cycle. For any occurrence of Stevens Johnson syndrome (toxic epidermal necrolysis), study therapy must be immediately and permanent discontinued.

12.8.5. Treatment

It is strongly recommended that subjects who develop dermatological reactions receive evaluations for management on the specific side effect.

Subjects should be encouraged to avoid exposure to sunlight. Broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with an SPF of at least 30 should be applied.

A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams (fluticasone prioprionate 0.5%), topical or systemic antibiotics, topical or systemic antihistamines and immunomodulators, and hypoallergenic moisturizers and emolliens for dry skin (5-10% urea in cetomacrogel cream or soft paraffin).

There is no standard treatment, known or established, that is proven effective for drug-related skin rashes or changes due to lapatinib. A **papulopustular** rash has been the most commonly observed skin adverse event, which frequently improves with an unchanged, uninterrupted dose of lapatinib therapy. The need for oral or topical antibiotics (minocycline, doxycicline, flucolaciclline or metronidazole cream) and topical steroids is a clinical decision of the investigator and, if indicated, a dermatology

consultation. For **pruritic** lesions oral antihistamine agents were reported successful. For **paronychia** antiseptic bath and local potent corticosteroids in addition to tetracycline therapy is recommended. If no improvement, a dermatology or surgery consultation is recommended. For **infected** lesions appropriate, culture driven, systemic or topical antibiotics are indicated.

Oral retinoids are not recommended because of theoretical concerns about negatively affecting the lapatinib mechanism of action and topical steroids result in irritation/severe dryness. Oral steroids may be used for a short treatment course (maximum of 14 days) which may help subjects to remain on study therapy.

For subjects with extensive or symptomatic NCI-CTCAE Grade 3 or 4 dermatologic event, or chronic, persistent or recurring lower grade skin events, dermatology consultation is encouraged. Upon consultation with a dermatologist, other treatment options (including immunomodulators such as topical tacrolimis or pimecrolimus) may be recommended for difficult to treat/unresponsive skin toxicities.

12.9. Appendix 9: Cockcroft and Gault Method for Calculated Creatinine Clearance

Creatinine clearance can be calculated from serum creatinine values by one of the two formulas below:

$$\text{Calculated creatinine clearance (mL/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/DL)}}$$

Female patients**:** multiply by 0.85

In order to use SI units for creatinine (μmol/L), the following formula may be used.

$$\text{Calculated creatinine clearance (mL/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight (kg)} \times 88.4}{72 \times 1 \times \text{serum creatinine (μmol/L))}}$$

Female patients**:** multiply by 0.85

Data Source: [Cockcroft, 1976]

12.10. Appendix 10 List of protocol Changes Changes

Note: deleted language is printed as ~~strikethrough~~ and added language is printed in **bold.**

12.10.1. Protocol Amendment 1

Global amendment: This version was amended to remove the third biopsy (based on the feedback from the countries). This version was the first one dispatched to the countries.

12.10.2. Protocol Amendment 2

Reason for change:

Description: The Primary Objective was updated to remove the evaluation of changes in the expression of biomarkers associated with HER family, apoptosis, and ABC transporters. The Primary Objective now evaluates the changes in the expression of biomarkers associated with immunomodulation.

Original text

All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal or any other reasons mentioned in section 4.2.1. The primary endpoint is to evaluate the changes in the expression of biomarkers associated with immunomodulation between the progression biopsy and the pre-treatment biopsy within each arm. Secondary efficacy endpoints include overall response rate; clinical benefit rate; and progression-free survival (PFS) on treatment; as well as safety/tolerability. Due to difficulty in enrolling subjects, enrollment will be halted and the study will be terminated early. No formal comparisons between treatment arms will be undertaken.

Amended Text

All subjects will receive study treatment until disease progression, **death,** unacceptable toxicity, ~~or~~ subject withdrawal **or any other reasons mentioned in section 4.2.1**~~, and after which, will be followed for subsequent anticancer therapy and disease progression events, and survival.~~ **The primary endpoint is to evaluate the changes in the expression of biomarkers associated with immunomodulation between the progression biopsy and the pre-treatment biopsy within each arm. Secondary efficacy endpoints include overall response rate; clinical benefit rate; and progression-free survival (PFS) on treatment; as well as safety/tolerability.** ~~The primary endpoint is to evaluate changes in the expression of biomarkers associated human epidermal growth factor receptor HER family or receptors and ligands, immunomodulation, apoptosis, and adenosine triphosphate binding cassette transporters in the progression biopsy compared with the pre-treatment biopsy within each arm. Key secondary biomarker and efficacy endpoints include overall survival; overall response rate; clinical benefit rate; progression-free survival (PFS); PFS subsequent lines of therapy; safety; and patients reported outcomes.~~ **Due to difficulty in enrolling subjects, enrollment will be halted and the study will be terminated early.** ~~It is estimated that approximately up to 225 subjects will be recruited into the study to achieve 50 evaluable~~

~~subjects (defined as subjects with a pre-treatment and progression biopsy with evaluable data for at least one biomarker) in each treatment arm.~~ No formal comparisons between treatment arms will be undertaken.

Reason for Change: List of Authors replaced by Novartis Study Team Members

Original Text

Author(s): [redacted]

Amended Text

Author(s): [redacted]

Reason for Change:

Revision Chronology of amendment was added for the first time.

Original Text

No Revision Chronology table

Amended Text

Revision Chronology:

2013N170247_0	**No publishing date**	**Amendment No. 0 (original version): This version was never dispatched to the countries.**
2013N170247_01	**26-MAR-2014**	**Amendment No. 01: Global amendment: This version was amended to remove the third biopsy (based on the feedback from the countries). This version was the first one dispatched to the countries.**
2013N170247_02	**23-Mar-2017**	**Amendment No. 02: Global amendment: Study EGF117165 is a post-approval commitment required by the CHMP to evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or**

chemotherapy. Recruitment of patients into study EGF117165 has been difficult. Efforts to boost recruitment were undertaken but the prospect to significantly improve recruitment is poor, thus preventing Novartis from meeting the agreed timelines for completion.

In addition, the results of this trial will likely become obsolete by the time of delayed completion. Therefore, Novartis proposes to terminate the study and to conduct a final analysis of the enrolled patients.

In this context, the updates to the protocol are as follows:
The Primary Objective was updated to remove the evaluation of changes in the expression of biomarkers associated with HER family, apoptosis, and ABC transporters. The Primary Objective now evaluates the changes in the expression of biomarkers associated with immunomodulation.

The Secondary Objectives were updated to remove OS and PFS on first next line and subsequent lines of anti-cancer therapies. The Patient Reported Outcomes (PRO) and Health-Related Quality of Life (HRQOL) were also removed.

[redacted]

Section 4.2.3 Subject Completion: Follow-up time was re-defined as follows: A subject will be considered to have completed the study if the subject presents with disease progression, starts a new anti-cancer therapy, dies or withdraws from the study, or the study ends, whichever comes first. In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

Reason for Change:

The contact information on the Sponsor Information Page was updated.

Original Text

Medical Monitor Contact Information: Dr [redacted]

[redacted]
E-mail: [redacted]
Telephone Number: [redacted]
Mobile Number: [redacted]

Amended Text

Dr. [redacted]

[redacted]
Novartis Pharma AG
Postfach
4002 Basel
Switzerland
Telephone: [redacted]

~~*Dr.*~~ [redacted]
[redacted]

~~E-mail:~~ [redacted]
~~Telephone Number:~~ [redacted]

~~Mobile Number:~~ [redacted]

Reason for Change

LIST OF ABBREVIATIONS was updated to remove abbreviations that are no longer applicable to this amendment

Original Text

ABC	Adenosine triphosphate binding cassette
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AI	Aromatase inhibitor
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
AR	Amphiregulin
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AV	Atrioventricular
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma-extra large
Bcl2L11	Bcl-2-like protein 11
β-HCG	beta human chorionic gonadotropin
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
BSA	Body surface area
BTC	β-cellulin
CAF	Cytokines and angiogenetic factors
CBR	Clinical benefit rate
cfDNA	Circulating free DNA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval

CISH	Chromogenic in situ hybridization
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DFS	Disease free survival
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EP	Evaluable Population
EPGN	Epigen
EPR	Epiregulin
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
FDR	False discovery rate
FISH	Fluorescence in situ hybridization
FDG-PET	fluorodeoxyglucose-positron emission tomography
FOXP3	Forkhead box P3
FSH	Follicle stimulating hormone
g/dL	Grams/deciLiter
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBEGF	Heparin-binding EGF-like growth factor
HER	Human epidermal growth factor receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQOL	Health Related Quality of Life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology System
ITT	Intent to Treat
IV	Intravenous(ly)
kg	Kilogram
L	Liter
LFT	Liver function test

LLN	Lower limit of normal
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
m^2	Meter squared
MAPK	Mitogen-activated protein kinase
MAF	Multidimensional Assessment of Fatigue Scale
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MSDS	Material Safety Data Sheet
MUGA	Multigated acquisition
MW	Molecular weight
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NRG	Neuregulin
OR	Odds ratio
ORR	Overall response rate
OTR	Optimally tolerated regimen
PAM	Prediction Analysis of Microarray
PAM50	Prediction Analysis of Microarray 50
PBMC	Peripheral blood mononuclear cells
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death 1
PDL-1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
PFS-NL	Progression-free survival on next-line therapy
PgR	Progesterone receptor
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PO	*Per os* (orally)
PR	Partial response
PRO	Patient reported outcomes
q3weekly	Every 3 weeks
QoL	Quality of life
QTcB	QT interval corrected for heart rate (Bazett's formula)
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SISH	Silver in situ hybridization
SPM	Study Procedures Manual
$t_{½}$	Half life
TDM-1	Trastuzumab emtansine
TGFα	Transforming growth factor α

TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRAIL	Tumor necrosis factor-related apoptosis-induced
TTP	Time to progression
ULN	Upper limit of normal
XIAP	X-linked inhibitor of apoptosis protein

Amended Text

ABC	Adenosine triphosphate binding cassette
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AI	Aromatase inhibitor
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
~~AR~~	~~Amphiregulin~~
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AV	Atrioventricular
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma-extra large
Bcl2L11	Bcl-2-like protein 11
β-HCG	beta human chorionic gonadotropin
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
BSA	Body surface area
BTC	β-cellulin
~~CAF~~	~~Cytokines angiogenetic factors~~
CBR	Clinical benefit rate
cfDNA	Circulating free DNA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
~~CTLA-4~~	~~Cytotoxic T-lymphocyte antigen 4~~
DFS	Disease free survival
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor

EMA	European Medicines Agency
EP	Evaluable Population
~~EPGN~~	~~Epigen~~
~~EPR~~	~~Epiregulin~~
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
~~FACT-B~~	~~Functional Assessment of Cancer Therapy-Breast~~
FDA	Food and Drug Administration
FDR	False discovery rate
FISH	Fluorescence in situ hybridization
FDG-PET	fluorodeoxyglucose-positron emission tomography
~~FOXP3~~	~~Forkhead box P3~~
FSH	Follicle stimulating hormone
g/dL	Grams/deciLiter
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBEGF	Heparin-binding EGF-like growth factor
HER	Human epidermal growth factor receptor
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
~~HRQOL~~	~~Health Related Quality of Life~~
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology System
ITT	Intent to Treat
IV	Intravenous(ly)
kg	Kilogram
L	Liter
LFT	Liver function test
LLN	Lower limit of normal
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
m^2	Meter squared
MAPK	Mitogen-activated protein kinase
~~MAF~~	~~Multidimensional Assessment of Fatigue Scale~~
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MSDS	Material Safety Data Sheet
MUGA	Multigated acquisition
MW	Molecular weight
NA	Not applicable

NCCN	National Comprehensive Cancer Network
NE	Not evaluable
~~NRG~~	~~Neuregulin~~
OR	Odds ratio
ORR	Overall response rate
OTR	Optimally tolerated regimen
PAM	Prediction Analysis of Microarray
PAM50	Prediction Analysis of Microarray 50
PBMC	Peripheral blood mononuclear cells
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death 1
PDL-1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
~~PFS-NL~~	~~Progression-free survival on next-line therapy~~
PgR	Progesterone receptor
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PO	*Per os* (orally)
PR	Partial response
~~PRO~~	~~Patient reported outcomes~~
q3weekly	Every 3 weeks
QoL	Quality of life
QTcB	QT interval corrected for heart rate (Bazett's formula)
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RAP	Reporting and analysis plan
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SISH	Silver in situ hybridization
SPM	Study Procedures Manual
$t_{½}$	Half life
TDM-1	Trastuzumab emtansine
TGFα	Transforming growth factor α
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
~~TRAIL~~	~~Tumor necrosis factor-related apoptosis-inducing ligand~~
TTP	Time to progression
ULN	Upper limit of normal
~~XIAP~~	~~X-linked inhibitor of apoptosis protein~~

Reason for Change

Protocol Summary-Rationale was updated for primary, secondary [redacted]

Original Text

This unusual PFS/OS pattern has been observed in two phase III trials of two different combinations of anti-HER 2 agents. A potential mechanistic hypothesis to explain the unusual PFS/OS pattern is that Dual blockade may exert be a "post-treatment effect" on subsequent therapies by modulating sensitivity to subsequent chemotherapy(ies) regimens.

Protocol EGF117165 is a phase II study designed to evaluate whether treatment with Dual blockade promotes changes to biomarkers associated with the HER2 family, immunomodulation, apoptosis, and adenosine triphosphate binding cassette (ABC) transporters. The biomarkers were selected due to the potential to correlate with altered the response to subsequent chemotherapy(ies) regimens.

Primary Objective:

- To evaluate changes in the expression of biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters between the pre-treatment and disease progression biopsy within each treatment arm.

Secondary Objectives:

- To describe overall response rate (ORR), clinical benefit rate (CBR), and PFS on study treatment and OS in subjects treated with trastuzumab in combination with lapatinib or chemotherapy.
- To describe PFS on first next line (PFS-NL) and subsequent lines of anti-cancer therapies.
- To explore association between changes in biomarkers and PFS, PFS-NL and OS.
- To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy.

[redacted]

- To describe the changes of Patient Reported Outcomes (PRO) and Health-Related Quality of Life (HRQOL) within the study population and to describe the differences of PRO /HRQOL between treatment groups.

[redacted]

Amended Text

This unusual PFS/OS pattern has been observed in two phase III trials of two different combinations of anti-HER 2 agents. A potential mechanistic hypothesis to explain the

unusual PFS/OS pattern is that Dual blockade may exert ~~be~~ a "post-treatment effect" on subsequent therapies by modulating sensitivity to subsequent chemotherapy(ies) regimens.

Protocol EGF117165 is a phase II study evaluating whether treatment with Dual blockade promotes changes of biomarkers associated with immunomodulation.

~~Protocol EGF117165 is a phase II study designed to evaluate whether treatment with Dual blockade promotes changes to biomarkers associated with the HER2 family, immunomodulation, apoptosis, and adenosine triphosphate binding cassette (ABC) transporters. The biomarkers were selected due to the potential to correlate with altered the response to subsequent chemotherapy(ies) regimens~~.

Primary Objective:

- To evaluate changes in the expression of biomarkers associated with ~~HER family,~~ immunomodulation~~, apoptosis, and ABC transporters between the pre-treatment and disease progression biopsy within each treatment arm.~~

Secondary Objectives:

- To describe overall response rate (ORR), clinical benefit rate (CBR), and PFS on study treatment ~~and OS~~ in subjects treated with trastuzumab in combination with lapatinib or chemotherapy.
- ~~To describe PFS on first next line (PFS-NL) and subsequent lines of anti-cancer therapies~~.
- ~~To explore association between changes in biomarkers and PFS, PFS-NL and OS.~~
- To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy.
- [redacted]
- ~~To describe the changes of Patient Reported Outcomes (PRO) and Health-Related Quality of Life (HRQOL) within the study population and to describe the differences of PRO /HRQOL between treatment groups.~~

[redacted]

[redacted]

Reason for Change:

Protocol Summary-Study Design was updated to remove the associated secondary objectives for the comparison of gene and/or protein expression. Survivals follow up after study discontinuation is removed. Also start date and stop date and progression on next line of anticancer therapy were removed.

Original Text

At disease progression a biopsy should be taken from the same site as the pre-treatment biopsy. The comparison of gene and/or protein expression changes in these biopsies will be the basis for the primary objective and associated secondary objectives.

All subjects will receive study treatment until disease progression, unacceptable toxicity, or subject withdrawal and will be followed for survival. After discontinuation of the study treatment, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected.

Approximately 225 subjects will be recruited into the study to achieve a total of 150 evaluable subjects, 50 evaluable subjects per arm.

Amended Text

At disease progression a biopsy should be taken from the same site as the pre-treatment biopsy. The comparison of gene and/or protein expression changes in these **paired** biopsies will be the basis for the primary objective**.** ~~and associated secondary objectives.~~

All subjects will receive study treatment until disease progression, **death,** unacceptable toxicity, ~~or~~ subject withdrawal **or any other reasons mentioned in section 4.2.1.** ~~and will be followed for survival. After discontinuation of the study treatment, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected.~~

~~Approximately 225 subjects will be recruited into the study to achieve a total of 150 evaluable subjects, 50 evaluable subjects per arm.~~

Reason for Change:

Protocol Summary-Study Assessment was updated to remove the broader assessment of changes in the expression of biomarkers associated with expression of HER family, apoptosis, and adenosine triphosphate binding cassette (ABC). Patient Reported Outcome (PRO) and the Health Related Quality of Life (HRQOL) assessment were removed.

Original Text

The primary endpoint is to analyze the changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters compared between the pre-treatment biopsy and disease progression biopsy. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately

Amended Text

The primary endpoint is to analyze the changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated with ~~HER family,~~ immunomodulation~~, apoptosis, and ABC transporters compared between the pre-treatment biopsy and disease progression biopsy~~. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately**.**

~~Patient reported outcomes assessments including health-related quality of life will be done on Day 1, Week 3, Week 12, and at the time of withdrawal from the study treatment.~~

Reason for Change:

Section 1.2.1 The reference of new trial PHEREXA was added.

Original Text:

A similar divergence of PFS and OS durations was reported in a study that evaluated pertuzumab combined with trastuzumab in the first-line treatment of MBC [Baselga 2012a].

Amended Text:

~~A similar divergence of PFS and OS durations was reported in a study that evaluated pertuzumab combined with trastuzumab in the first-line treatment of MBC [Baselga 2012a].~~ **Similar divergence of PFS and OS durations was reported in the large phase III Cleopatra [Baselga 2012a] and PHEREXA [Urruticoechea 2016] trials evaluating dual HER2 blockade (pertuzumab plus trastuzumab) in HER2-positive MBC.**

Reason for Change:

Section 1.2.2 The original text was revised according to the changes in the secondary endpoints (excluding OS assessment). Some editorial changes were added for the description of the HER2-enriched and non-HER2 enriched subgroups.

Original Text

Therefore, this study will also enroll standard HER2 positive subjects as defined by standard histopathologic criteria with a non-HER2 enriched subtype that will be assigned to treatment with lapatinib in combination with trastuzumab.

Amended Text

Therefore, this study will also enroll standard HER2 positive subjects as defined by standard histopathologic criteria **with a non-HER2 enriched subtype** that will be assigned to treatment with lapatinib in combination with trastuzumab. ~~In this HER2-positive, non-HER2 enriched (i.e. luminal A, luminal B and basal-like) population, the study will investigate any biomarker changes associated with long-term benefit that may be inclusive of all HER2 positive subjects as well as those that may be specific to the HER2-enriched molecular subtype.~~

Reason for Change:

1.2.3 Updated to state that based on emerging data the focus of the study will be immunomodulation markers.

Original Text

1.2.3. Mechanisms to Investigate the Benefit of Dual blockade on Subsequent Lines of Therapy. Immunomodulation by Dual blockade as a putative mechanism affecting response to subsequent lines of therapy

The EGF104900 study population was heavily pretreated, with a median of 6 prior chemotherapeutic agents; as is standard in the treatment of breast cancer, the types of agents received were of different mechanistic classes (e.g., taxanes, anthracyclines, and alkylating agents). Breast cancers may evade the therapeutic effects of these chemotherapies through intrinsic mechanisms, acquisition of genetic aberrations, or activation of compensatory pathways that provide a selective advantage and render the tumor resistant. The primary mechanisms of resistance in this population are postulated to be broad, and resistance is assumed to be multifactorial, involving mechanisms that include direct/within-tumor effects and indirect/extrinsic effects [O'Connor 2009].

The primary hypothesis under evaluation in this study is that the chemotherapy-free period during which subjects receive treatment with Dual blockade in effect reverses resistance to chemotherapy, thus conferring the disease sensitive to subsequent anticancer therapy. This suggests that the approach to elucidating the mechanisms or pathways by which Dual blockade reverses resistance to chemotherapy should be directed toward generalized mechanisms. There are no validated markers of resistance to chemotherapeutic agents; therefore, the primary objective will focus on 4 mechanisms that have been described to impact response to chemotherapy.

Amended Text

1.2.3 ~~Mechanisms to Investigate the Benefit of Dual blockade on Subsequent Lines of Therapy~~ Immunomodulation by Dual blockade as a putative mechanism affecting response to subsequent lines of therapy

The EGF104900 study population was heavily pretreated, with a median of 6 prior chemotherapeutic agents; as is standard in the treatment of breast cancer, the types of agents received were of different mechanistic classes (e.g., taxanes, anthracyclines, and alkylating agents). **The chemotherapy-free period during which subjects received treatment with Dual blockade in EGF104900 may have reversed resistance to chemotherapy, thus conferring the disease sensitive to subsequent anticancer therapy.**

There is now mounting evidence that a pre-existing immunologic response might enhance the effects of conventional cytotoxic chemotherapy and HER2 targeted therapy in early HER2+ breast cancer [Denkert 2010, Issa-Nummer 2013, Denkert 2015, Ignatiadis 2012, Loi 2013, Loi 2014] and anti-HER2 therapies seem to be able to engage the immune system in different ways. For instance, pre-clinical data suggest that Lapatinib enhances T-cell and IFN-γ-based immunity and affects the myeloid infiltrate (i.e. tumor-associated macrophages and monocytes) in tumors [Hannesdóttir 2013, Laoui 2013]. Emerging data from the neoadjuvant setting provide useful insights on molecular changes induced by HER2-targeted neoadjuvant treatment and recent studies are suggesting that single HER2 targeted agents and Dual blockade of the HER2 receptor induce changes in immune markers and the tumor microenvironment [Bianchini 2016, Dieci 2015]. The Neosphere trial showed that HER2 targeted agents and dual HER2 blockade modulate the amount of tumor infiltrating lymphocytes (TIL) - a surrogate biomarker of pre-existing host antitumour immunity - and the expression levels of selected mRNA immune markers [Bianchini 2016]. The investigators were also able to show that these patient-level immune modulations are linked to distant event free survival and the differential changes in stromal TILS (sTIL) levels actually seem to carry more prognostic information than either pre-or post-treatment sTIL levels.

Tumors with increased numbers of TIL after treatment may be able to elicit an antitumor immune response and may have a particularly strong response to subsequent treatment lines, as the immune cells may have been already sensitized against some tumor antigens before the onset of chemotherapy and therefore enhance the ability of chemotherapy to eliminate cancer cells. Immunomodulation by dual HER2 blockade is a plausible mechanism how molecular changes could help to overcome resistance to chemotherapeutic agents, eventually leading to increased clinical activity and augmented response seen in overall survival.

The primary hypothesis under evaluation in this study is that the chemotherapy-free period during which subjects receive treatment with Dual blockade modulates the immune microenvironment, which in turn may influence the efficacy of sequential treatment. A recent study just revealed a comparable distribution and composition of infiltrating lymphocyte subtypes in metastasis when compared to the matched primary tumor [Sobottka 2016]. This pattern was found regardless of the anatomical site at which the metastasis had occurred, suggesting that primary tumor shapes the infiltrating immune cell composition rather than the metastases

with their local immunity [Sobottka 2016]. The EGF11765 study will support a better understanding if the rapidly accumulating evidence for the importance of the immune microenvironment in HER2-positive breast cancer and the observed immunomodulation in the neoadjuvant setting can be confirmed in the advanced setting and support the putative mechanism of action of HER2 dual blockade and its potential function on the tumor microenvironment.
~~Breast cancers may evade the therapeutic effects of these chemotherapies through intrinsic mechanisms, acquisition of genetic aberrations, or activation of compensatory pathways that provide a selective advantage and render the tumor resistant. The primary mechanisms of resistance in this population are postulated to be broad, and resistance is assumed to be multifactorial, involving mechanisms that include direct/within-tumor effects and indirect/extrinsic effects [O'Connor, 2009].~~

~~The primary hypothesis under evaluation in this study is that the chemotherapy-free period during which subjects receive treatment with Dual blockade in effect reverses resistance to chemotherapy, thus conferring the disease sensitive to subsequent anticancer therapy. This suggests that the approach to elucidating the mechanisms or pathways by which Dual blockade reverses resistance to chemotherapy should be directed toward generalized mechanisms. There are no validated markers of resistance to chemotherapeutic agents; therefore, the primary objective will focus on 4 mechanisms that have been described to impact response to chemotherapy.~~

Reason for Change:

Section 1.2.3.1 on HER family of receptor and ligands, Section 1.2.3.2 on Immunomodulation, Section 1.2.3.3 on Apoptosis and Section 1.2.3.4 on ABC transporters and drug efflux pumps were all removed because section 1.2.3 was re-written to focus on immune markers moving forward.

Original Text:

1.2.3.1 HER Family of Receptors and Ligands

EGFR, HER2, HER3, and HER4 are the 4 members comprising the family of Type I receptor tyrosine kinases. These receptors share common structural and functional elements including an extracellular domain that consists of 4 subdomains involved in ligand binding (domain I, III) and in dimerization (domain II) and an intracellular tyrosine kinase domain. Ligands have been identified for EGFR, HER3, and HER4, whereas no ligand has been identified for HER2. Of the 11 ligands identified (amphiregulin [AR], β-cellulin [BTC], epidermal growth factor [EGF], epigen [EPGN], epiregulin [EPR], heparin-binding EGF-like growth factor [HBEGF], transforming growth factor α [TGFα], and neuregulin [NRG1, NRG2, NRG3, and NRG4]), the majority are not specific for 1 receptor [Yarden, 2012]. Ligand binding to HER receptor(s) induces receptor dimerization, resulting in the formation of homodimers or heterodimers, with HER2 as the preferred heterodimerization partner due to its role in increasing receptor-ligand affinity and potentiating HER-mediated signalling. HER signalling is also activated through a ligand-independent mechanism, an example of which is HER2 homodimers, whereby overexpression of HER2 generates their formation.

The HER receptor combination potential and repertoire of HER ligands as well as ligand-independent mechanisms suggest a diverse signalling capacity for this family of receptors [Olayioye 2000].

Several preclinical and clinical studies have demonstrated an association between response to certain types of chemotherapies as well as HER2-directed agents and the expression of HER receptors or their associated ligands.

HER2 overexpression was observed to be associated with intrinsic resistance to DNA damaging agents and paclitaxel potentially owing in part to the role of HER2 signalling in regulating cell cycle and survival [Tan, 2000]. A common standard of care for the treatment of HER2-positive breast cancer is chemotherapy in combination with HER2-directed agents; mechanisms that adversely impact the efficacy of these agents may affect the efficacy of chemotherapy. Therefore, as evidence supports a role for the expression of HER receptors and ligands in mediating response to HER2-directed agents such as trastuzumab and lapatinib [Arteaga, 2006; Ritter, 2007; Amin, 2010], treatment with Dual blockade may be a more effective treatment than either agent alone due to complementary mechanisms of action [Scaltriti, 2009; Ghosh, 2007; Maruyama, 2011; Sanchez-Martin, 2012].

The expression of HER receptors EGFR, HER2, HER3, and HER4 and their associated ligands will be measured by gene expression analyses. The protein expression levels of the HER receptors will also be measured by IHC.

1.2.3.2. Immunomodulation

The concept of tumor escape as a process of immunoediting involves the acquisition of adaptations that allow the tumor to evade detection and destruction by the immune system. The mechanism by which tumor escape occurs is through induction of immune tolerance or inhibition of tumor recognition and resistance to killing by activated immune effector cells [Vesely, 2011]. Immunoediting may affect response to chemotherapy, as some chemotherapies induce immunogenic cell death and stimulate a secondary antitumor immune response [Kroemer, 2013].

Alteration of expression of immune checkpoint proteins, such as programmed cell death 1 ligand 1 (PDL-1), programmed cell death 1(PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and forkhead box P3 (FOXP3), a transcription factor expressed in regulatory T cells and involved in their suppressive function, may provide a mechanism by which the tumor cells evade the immune system [Melero, 2013; Huehn, 2009]. The expression of these proteins in addition to the expression of different subpopulations of tumor-infiltrating lymphocytes, natural killer cells, and macrophages will be measured by gene expression profiling and IHC.

Several gene signatures, or metagenes, have been developed as surrogate representatives of immune function [Rody, 2009; Hanker, 2013; Nagalla, 2013]. The metagene signature from Nagalla et al. was developed through an integrated dataset of 1954 clinically annotated breast tumor expression profiles to investigate the relationship between immunity and proliferation. From these analyses, 3 distinct clusters with annotated immune function were defined and further postulated to reflect different tumor-

infiltrating leukocyte populations: B cells/plasma cells, T cells/natural killer cells, and monocytes/dendritic cells. These metagene clusters or other development signatures may be evaluated as part of the primary objective.

1.2.3.3. Apoptosis

Alterations in the apoptotic pathways through inactivation of pro-apoptotic factors and overexpression of pro-survival factors have been implicated in resistance to chemotherapeutics, as these agents elicit their effect through activation of tumor cell death [O'Connor, 2009; Rebucci, 2013].

B-cell lymphoma 2 (Bcl-2) and the family member B-cell lymphoma-extra large (Bcl-xl) will be evaluated in this study, as they are key anti-apoptotic factors. Additional anti-apoptotic factors under evaluation include survivin (baculoviral inhibitor of apoptosis repeat-containing 5 [BIRC5]) and X-linked inhibitor of apoptosis protein (XIAP). BIM (Bcl-2-like protein 11[Bcl2L11]), p53, and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) also will be evaluated, as they are key factors involved in activation of apoptotic pathways. The expression of these factors will be measured by gene expression analysis and IHC if validated assays are available.

1.2.3.4. ABC Transporters/Drug Efflux Pumps

Adenosine triphosphate binding cassette (ABC) proteins comprise a large family of transporters with a wide variety of substrates, such as the multidrug resistance 1 protein (ABCB1), breast cancer resistance protein (ABCG2), and multidrug resistance-related protein (ABCC1), all of which have been shown to promote de novo and acquired resistance to multiple chemotherapeutic agents with varying mechanisms of action. This study will evaluate the expression of these specific ABC transporters, as they have been purported to have the greatest therapeutic relevance for treatment of many common malignancies [O'Connor, 2009].

Amended Text:

~~HER Family of Receptors and Ligands~~

~~EGFR, HER2, HER3, and HER4 are the 4 members comprising the family of Type I receptor tyrosine kinases. These receptors share common structural and functional elements including an extracellular domain that consists of 4 subdomains involved in ligand binding (domain I, III) and in dimerization (domain II) and an intracellular tyrosine kinase domain. Ligands have been identified for EGFR, HER3, and HER4, whereas no ligand has been identified for HER2. Of the 11 ligands identified (amphiregulin [AR], β-cellulin [BTC], epidermal growth factor [EGF], epigen [EPGN], epiregulin [EPR], heparin-binding EGF-like growth factor [HBEGF], transforming growth factor α [TGFα], and neuregulin [NRG1, NRG2, NRG3, and NRG4]), the majority are not specific for 1 receptor [, 2012]. Ligand binding to HER receptor(s) induces receptor dimerization, resulting in the formation of homodimers or heterodimers, with HER2 as the preferred heterodimerization partner due to its role in increasing~

~~receptor-ligand affinity and potentiating HER-mediated signalling. HER signalling is also activated through a ligand-independent mechanism, an example of which is HER2 homodimers, whereby overexpression of HER2 generates their formation. The HER receptor combination potential and repertoire of HER ligands as well as ligand-independent mechanisms suggest a diverse signalling capacity for this family of receptors [, 2000].~~

~~Several preclinical and clinical studies have demonstrated an association between response to certain types of chemotherapies as well as HER2-directed agents and the expression of HER receptors or their associated ligands.~~

~~HER2 overexpression was observed to be associated with intrinsic resistance to DNA-damaging agents and paclitaxel potentially owing in part to the role of HER2 signalling in regulating cell cycle and survival [Tan, 2000]. A common standard of care for the treatment of HER2-positive breast cancer is chemotherapy in combination with HER2-directed agents; mechanisms that adversely impact the efficacy of these agents may affect the efficacy of chemotherapy. Therefore, as evidence supports a role for the expression of HER receptors and ligands in mediating response to HER2-directed agents such as trastuzumab and lapatinib [Arteaga, 2006; Ritter, 2007; Amin, 2010], treatment with Dual blockade may be a more effective treatment than either agent alone due to complementary mechanisms of action [Scaltriti, 2009; Ghosh, 2007; Maruyama, 2011; Sánchez-Martín, 2012].~~

~~The expression of HER receptors EGFR, HER2, HER3, and HER4 and their associated ligands will be measured by gene expression analyses. The protein expression levels of the HER receptors will also be measured by IHC.~~

~~Immunomodulation~~

~~The concept of tumor escape as a process of immunoediting involves the acquisition of adaptations that allow the tumor to evade detection and destruction by the immune system. The mechanism by which tumor escape occurs is through induction of immune tolerance or inhibition of tumor recognition and resistance to killing by activated immune effector cells [, 2011]. Immunoediting may affect response to chemotherapy, as some chemotherapies induce immunogenic cell death and stimulate a secondary antitumor immune response [, 2013].~~

~~Alteration of expression of immune checkpoint proteins, such as programmed cell death 1 ligand 1 (PDL-1), programmed cell death 1(PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and forkhead box P3 (FOXP3), a transcription factor expressed in regulatory T cells and involved in their suppressive function, may provide a mechanism by which the tumor cells evade the immune system [, 2013; , 2009]. The expression of these proteins in addition to the expression of different subpopulations of tumor-infiltrating lymphocytes, natural killer cells, and macrophages will be measured by gene expression profiling and IHC.~~

~~Several gene signatures, or metagenes, have been developed as surrogate representatives of immune function [, 2009; , 2013; , 2013]. The metagene signature from Nagalla et al. was developed through an integrated dataset of 1954 clinically annotated breast tumor-~~

~~expression profiles to investigate the relationship between immunity and proliferation. From these analyses, 3 distinct clusters with annotated immune function were defined and further postulated to reflect different tumor-infiltrating leukocyte populations: B cells/plasma cells, T cells/natural killer cells, and monocytes/dendritic cells. These metagene clusters or other development signatures may be evaluated as part of the primary objective.~~

~~Apoptosis~~

~~Alterations in the apoptotic pathways through inactivation of pro-apoptotic factors and overexpression of pro-survival factors have been implicated in resistance to chemotherapeutics, as these agents elicit their effect through activation of tumor cell death [, 2009; Rebucci, 2013].~~

~~B-cell lymphoma 2 (Bcl-2) and the family member B-cell lymphoma-extra large (Bcl-xl) will be evaluated in this study, as they are key anti-apoptotic factors. Additional anti-apoptotic factors under evaluation include survivin (baculoviral inhibitor of apoptosis repeat-containing 5 [BIRC5]) and X-linked inhibitor of apoptosis protein (XIAP). BIM (Bcl-2-like protein 11[Bcl2L11]), p53, and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) also will be evaluated, as they are key factors involved in activation of apoptotic pathways. The expression of these factors will be measured by gene expression analysis and IHC if validated assays are available.~~

~~ABC Transporters/Drug Efflux Pumps~~

~~Adenosine triphosphate binding cassette (ABC) proteins comprise a large family of transporters with a wide variety of substrates, such as the multidrug resistance 1 protein (ABCB1), breast cancer resistance protein (ABCG2), and multidrug resistance-related protein (ABCC1), all of which have been shown to promote de novo and acquired resistance to multiple chemotherapeutic agents with varying mechanisms of action. This study will evaluate the expression of these specific ABC transporters, as they have been purported to have the greatest therapeutic relevance for treatment of many common malignancies [, 2009].~~

Reason for Change

Section 1.2.4 Hypothesis Based on emerging data, the focus of the study will be based on immunomodulation markers only

Original Text

It is postulated that treatment with Dual blockade (lapatinib in combination with trastuzumab) will cause molecular changes in at least 1 of 4 biomarker groups that may sensitize tumors to subsequent post-study therapies. Furthermore, the sensitization to subsequent post-study therapies is expected to result in an OS benefit. The primary endpoint of the study will be to evaluate changes in expression of biomarkers associated with the HER family or receptors and ligands, immunomodulation, apopotsis, and ABC transports between a pre-treatment biopsy and the disease progression biopsy.

This Phase II study will evaluate potential mechanisms to explore the antitumor activity of dual blockade and gain insight into the observed post-study treatment effect on survival in EGF104900. In addition, it will provide a descriptive clinical outcome for subjects treated with trastuzumab in combination with lapatinib or chemotherapy.

Amended Text

It is postulated that treatment with Dual blockade (lapatinib in combination with trastuzumab) ~~will~~ **may** cause molecular changes ~~in at least 1 of 4 biomarker groups~~ that may sensitize tumors to subsequent post-study therapies. **As discussed above, based on emerging data the focus will be on immunomodulation markers**. ~~Furthermore, the sensitization to subsequent post-study therapies is expected to result in an OS benefit.~~ The primary endpoint of the study will be to evaluate changes in expression of biomarkers associated with ~~the HER family or receptors and ligands,~~ immunomodulation~~apopotsis, and ABC transports between a pre-treatment biopsy and the disease progression biopsy.~~

This Phase II study will evaluate potential mechanisms **related to immunomodulation** to explore the antitumor activity of dual blockade and gain insight into the observed post-study treatment effect on survival in EGF104900. In addition, it will provide a descriptive clinical outcome for subjects treated with trastuzumab in combination with lapatinib or chemotherapy.

Reason for Change:

Section 1.3.3 Usage of various cancers was removed for the development of lapatinib

Original Text:

Lapatinib is a tyrosine kinase inhibitor that is being developed for various cancers, including MBC.

Amended Text:

Lapatinib is a tyrosine kinase inhibitor that is **indicated in the treatment of** ~~being developed for various cancers, including~~ MBC.

Reason for Change:

Section 2 OBJECTIVES AND ENDPOINTS The Primary Object was updated to remove the study of changes in biomarkers associated with the HER2 family, apoptosis, adenosine triphosphate binding cassette (ABC) transporters.

The Secondary Objective was updated to remove OS, PFS on first next line and subsequent lines of anti-cancer therapies. Patient Reported Outcomes (PRO) and Health-Related Quality of Life (HRQOL) was also removed

[redacted]

Original Text:

Objectives	Endpoints
Primary	
• To evaluate changes in the expression of biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters within each treatment arm between the pre-treatment biopsy and the disease progression biopsy.	• Changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters compared between the pre-treatment biopsy and disease progression biopsy. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately.
Secondary	
• To describe, ORR, CBR, and PFS on study treatment and OS in subjects treated with trastuzumab in combination with lapatinib or chemotherapy. • To describe PFS on first next line (PFS-NL) and subsequent lines of anti-cancer therapies. • To explore association between changes in biomarkersand PFS, PFS-NL and OS. • To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy. [redacted] • To describe changes of Patient Reported Outcomes (PRO)(Health Related Quality of Life (HRQOL)) within the study population and to describe the differences of PRO/HRQOL between treatment groups.	• OS defined as the interval of time between randomization and death due to any cause; investigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months • PFS on all subsequent lines of anti-cancer therapies defined as the interval of time between start of next-line anticancer therapy and disease progression or discontinuation of that next-line therapy for any cause • Determine if a change at disease progression in biomarker correlates with PFS, PFS-NL or OS • Summary AE profile for both treatment arms [redacted] • Summarize the results of the Functional Assessment of Cancer Therapy – Breast (FACT-B) and Multidimensional Assessment of Fatigue (MAF) Scalefor each arm
[redacted]	
Abbreviations: ABC, adenosine triphosphate binding cassette; AE, adverse event; CBR, clinical benefit rate; CR, complete response; HER, human epidermal growth factor receptor; [redacted]	

Objectives	Endpoints
PD, progressive disease; PFS, progression-free survival; PFS-NL, progression-free survival on next-line therapy; PR, partial response; ORR, overall response rate; OS, overall survival; SD, stable disease.	

Amended Text:

Objectives	Endpoints
Primary	
• To evaluate changes in the expression of biomarkers associated with ~~HER family,~~ immunomodulation, ~~apoptosis, and ABC transporters within each treatment arm between the pre-treatment biopsy and the disease progression biopsy~~.	• Changes in gene and/or protein expression profile within each arm on a prespecified set of biomarkers associated **with** ~~with HER family,~~ immunomodulation~~, apoptosis, and ABC transporters compared~~ between the pre-treatment biopsy and disease progression biopsy. The HER2-enriched and Non-HER2-enriched cohorts will be analyzed separately.
Secondary	
• To describe ORR, CBR, and PFS on study treatment ~~and OS~~ in subjects treated with trastuzumab in combination with lapatinib or chemotherapy. • ~~To describe PFS on first next line (PFS-NL) and subsequent lines of anti-cancer therapies.~~ • **To explore association between changes** in biomarkersand PFS, ~~PFS-NL and OS.~~ • To describe the safety and tolerability of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy. [redacted] • ~~To describe changes of Patient Reported Outcomes (PRO)(Health Related Quality of Life (HRQOL)) within the study population and to describe the differences of PRO/HRQOL between treatment groups.~~	• OS defined as ~~the interval of time between randomization and death due to any cause;~~ investigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months • ~~PFS on all subsequent lines of anti-cancer therapies defined as the interval of time between start of next-line anticancer therapy and disease progression or discontinuation of that next-line therapy for any cause~~ • ~~Determine~~ **Describe** if a change at disease progression in biomarker correlates with PFS, ~~PFS-NL or OS~~ • Summary AE profile for both treatment arms [redacted] Summarize ~~the results of the Functional Assessment of Cancer Therapy – Breast (FACT-B) and Multidimensional Assessment of Fatigue (MAF) Scalefor each arm~~
[redacted]	

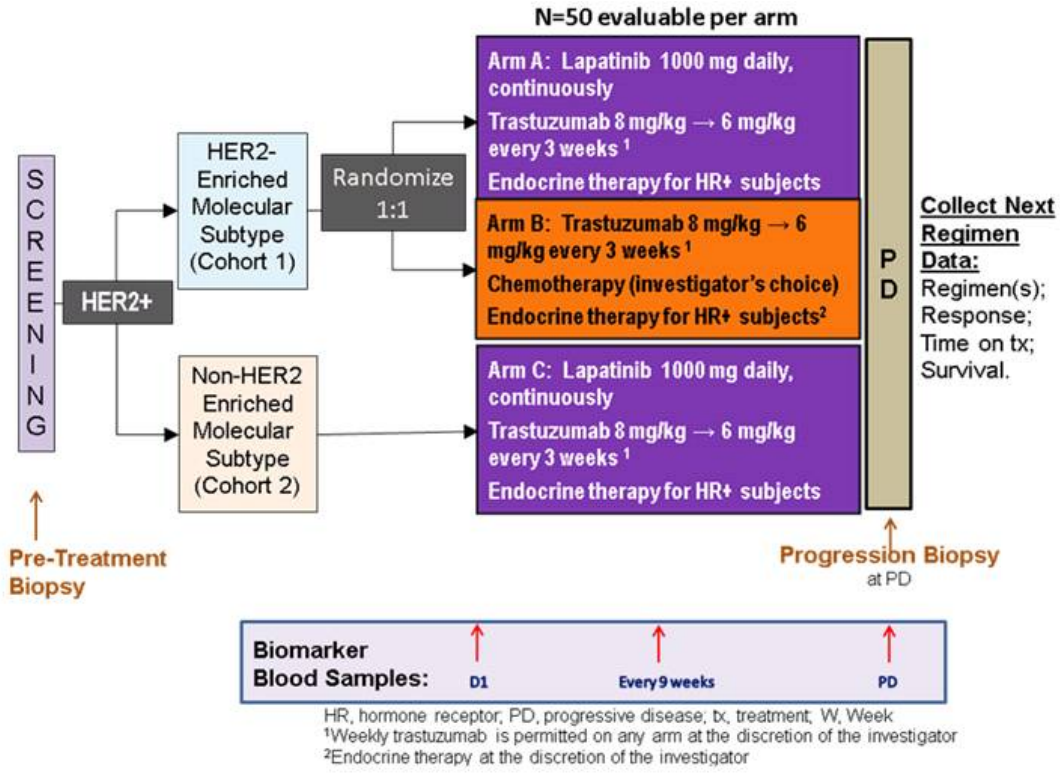
[redacted]

Abbreviations: ~~ABC, adenosine triphosphate binding cassette;~~ AE, adverse event; CBR, clinical benefit rate; CR, complete response; HER, human epidermal growth factor receptor; [redacted] PD, progressive disease; PFS, progression-free survival; ~~PFS NL, progression free survival on next line therapy~~; PR, partial response; ORR, overall response rate; ~~OS, overall survival;~~ SD, stable disease.

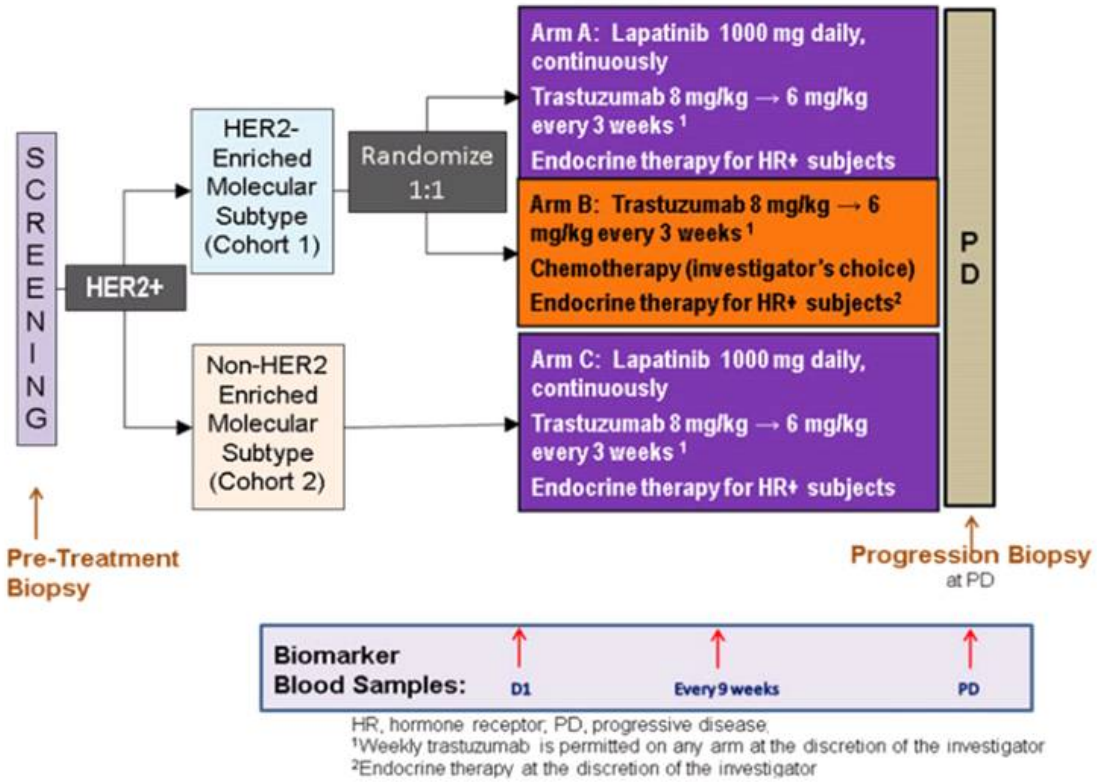
Reason for change

Section 3 Study Design schema figure was updated to remove the number of evaluable patient per arm and data collection on the next regimen and survival.

Original Text



Amended Text



Reason for Change

Section 3 Subject Completion: Follow-up time was re-defined as follows: A subject will be considered to have completed the study if the subject presents with disease progression, starts a new anti-cancer therapy, dies or withdraws from the study, or the study ends, whichever comes first. In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. The data cutoff and end of study are defined.

Original Text

Biopsies of a metastatic site will be collected at two timepoints: screening (pre-treatment) and at disease progression (progression). The primary objective is to evaluate changes in biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters between the pre-treatment biopsy and the progression biopsy within each arm. Radiologic disease assessments will be performed every 9 weeks until 54 weeks then every 24 weeks thereafter until disease progression or withdrawal from study treatment for any reason. [redacted]

Safety assessments including physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs and weight, adverse event (AE)

monitoring, and laboratory tests (complete blood count, blood chemistry including liver function test) will be done at screening and then every 3 weeks for the duration of therapy. Additional safety assessments, such as cardiac monitoring, are required for all subjects every 12 weeks until discontinuation from the study therapy.

All subjects will receive study treatment until disease progression, unacceptable toxicity, or subject withdrawal of consent. After discontinuation of the study treatment, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected.

It is estimated that approximately 85% of subjects will discontinue study treatment due to disease progression and of these, 80% will have evaluable paired tumor biopsies. Therefore, to achieve a total of 150 evaluable subjects, 50 evaluable subjects in each treatment arm, approximately 225 subjects may be recruited into the study.

After discontinuation from study treatment, subjects will be followed for subsequent disease progressions and overall survival until all criteria below are met:

- 75% of the subjects have died
- 100% of subjects have completed study treatment;
- all subjects who go onto first next line therapy have completed first next line therapy.

During survival follow-up, information on all post-study anticancer therapies will be collected, including generic name, regimen number, start date, stop date, reason for discontinuing post-study treatment anticancer therapy regimen, date of disease progression (clinical and/or radiologic if applicable), and number of cycles/doses until death or conclusion of the study.

At the time any arm accrues 50 evaluable subjects (Arms A and B will require both to have accrued 50 evaluable subjects each), that arm(s) will be closed to further enrollment. It is expected that the Non-HER2-enriched Dual blockade arm will accrue 50 evaluable subjects prior to the HER2-enriched arms.

When an arm or arms is closed to further enrollment, GSK will notify all investigators in writing. Subjects who have signed consent prior to receipt of the written notification, if determined eligible for a cohort (HER2-enriched or Non-HER2-enriched) to which treatment arm(s) is closed, will be permitted to continue in the study.

Subjects signing consent after receipt of written notification and who are allocated to a cohort where the treatment arm(s) is closed will be considered screen failures for the remaining open cohort (see Section 4.3).

Amended Text

Biopsies of a metastatic site will be collected at two timepoints: screening (pre-treatment) and at disease progression (progression). The primary objective is to evaluate changes in biomarkers associated with ~~HER family,~~ immunomodulation, ~~apoptosis, and ABC transporters~~ between the pre-treatment biopsy and the progression biopsy within each arm. Radiologic disease assessments will be performed every 9 weeks until 54 weeks then every 24 weeks thereafter until disease progression, **death**, or withdrawal from study treatment for any reason **(e.g. unacceptable toxicity).** [redacted]

Safety assessments including physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs and weight, adverse event (AE) monitoring, and laboratory tests (complete blood count, blood chemistry including liver function test) will be done at screening and then every 3 weeks for the duration of therapy. Additional safety assessments, such as cardiac monitoring, are required for all subjects every 12 weeks until discontinuation from the study therapy.

All subjects will receive study treatment until disease progression, death, unacceptable toxicity, ~~or~~ subject withdrawal of consent **or any other reasons mentioned in section 4.2.1.**
In case of disease progression during the treatment period, the ~~patient~~subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out ~~in the protocol~~; the ~~patient~~subject will be considered as having completed the study.
Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out ~~in the protocol~~; the ~~patient~~subject will be considered as having completed the study.

In case of ~~stopping~~study treatment discontinuation for any reasons ~~in the absence of~~other than disease progression, the ~~patient~~subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

The data cut-off for the primary analysis will be defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier. Following the cut-off date for the primary analysis, the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:
- **All patients have died or discontinued from the study**

- **Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study**
- **At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.**

~~After discontinuation of the study treatment, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected~~

Due to difficulty in enrolling subjects into this trial, future enrolment will be halted and the study will be terminated early.

~~It is estimated that approximately 85% of subjects will discontinue study treatment due to disease progression and of these, 80% will have evaluable paired tumor biopsies. Therefore, to achieve a total of 150 evaluable subjects, 50 evaluable subjects in each treatment arm, approximately 225 subjects may be recruited into the study.~~

~~After discontinuation from study treatment, subjects will be followed for subsequent disease progressions and overall survival until all criteria below are met:~~

- ~~75% of the subjects have died~~
- ~~100% of subjects have completed study treatment;~~
- ~~all subjects who go onto first next line therapy have completed first next line therapy.~~

~~During survival follow-up, information on all post-study anticancer therapies will be collected, including generic name, regimen number, start date, stop date, reason for discontinuing post-study treatment anticancer therapy regimen, date of disease progression (clinical and/or radiologic if applicable), and number of cycles/doses until death or conclusion of the study.~~

~~At the time any arm accrues 50 evaluable subjects (Arms A and B will require both to have accrued 50 evaluable subjects each), that arm(s) will be closed to further enrollment. It is expected that the Non-HER2-enriched Dual blockade arm will accrue 50 evaluable subjects prior to the HER2-enriched arms.~~

When an arm or arms is closed to further enrollment, GSK will notify all investigators in writing. **At the time of stopping the enrollment, the sponsor will notify all the investigators in writing.** Subjects who have signed consent prior to receipt of the written notification, if determined eligible for a cohort (HER2-enriched or Non-HER2-enriched) ~~to which treatment arm(s) is closed,~~ will be permitted to continue in the study.

~~Subjects signing consent after receipt of written notification and who are allocated to a cohort where the treatment arm(s) is closed will be considered screen failures for the remaining open cohort (see Section 4.3).~~

Reason for Change

Section 3.1 Discussion of biomarkers was updated to remove HER2 family, apoptosis, and adenosine triphosphate binding cassette (ABC)

Original Text
This study is a post-approval commitment with regulatory authorities. It is designed with the primary endpoint to evaluate the changes in biomarkers associated with HER family, immunomodulation, apoptosis, and ABC transporters between the pre-treatment and disease progression biopsy. It is hypothesized that these changes in biomarkers may modulate resistance mechanisms and thereby alter the response to subsequent chemotherapy based regimens. Therefore, in addition to the description of the clinical outcome of ORR, CBR, PFS and OS for each arm, PFS on next-line therapies will be collected and summarized for each arm.

… Therefore, this study will also enroll a standard HER2 positive population as defined by standard histopathologic criteria that will be assigned to treatment with lapatinib in combination with trastuzumab. In this HER2 positive, non-HER2 enriched (i.e. luminal A, luminal B and basal-like) population, the study will investigate any biomarker changes associated with long-term benefit that may be inclusive of all HER2 positive patients as well as those that may be specific to the HER2-enriched molecular subtype. Both cohorts will be treated with dual blockade (trastuzumab in combination with lapatinib). The inclusion of these two cohorts was discussed and agreed upon with the scientific advice working party of the Committee for Medicinal Products for Human Use (CHMP).

In addition, common clinical practice in these heavily pretreated patients is to continue trastuzumab in combination with chemotherapy. As such, the effect of dual blockade and trastuzumab plus chemotherapy in the HER2-enriched cohort will be evaluated in this study

Amended Text
This study is a post-approval commitment with regulatory authorities. It is designed with the primary endpoint to evaluate the changes in biomarkers associated with ~~HER family,~~ immunomodulation~~, apoptosis, and ABC transporters~~ between the pre-treatment and disease progression biopsy. ~~It is hypothesized that these changes in biomarkers may modulate resistance mechanisms and thereby alter the response to subsequent chemotherapy based regimens. Therefore, in addition to the description of the clinical outcome of ORR, CBR, PFS and OS for each arm, PFS on next-line therapies will be collected and summarized for each arm.~~

… Therefore, this study will also enroll a standard HER2 positive population as defined by standard histopathologic criteria **with non-HER2-enriched subtype** that will be assigned to treatment with lapatinib in combination with trastuzumab. ~~In this HER2 positive, non-HER2 enriched (i.e. luminal A, luminal B and basal-like) population, the~~

~~study will investigate any biomarker changes associated with long-term benefit that may be inclusive of all HER2 positive patients as well as those that may be specific to the HER2-enriched molecular subtype.~~ Both cohorts will be treated with dual blockade (trastuzumab in combination with lapatinib). The inclusion of these two cohorts was discussed and agreed upon with the scientific advice working party of the Committee for Medicinal Products for Human Use (CHMP).

~~In addition, common clinical practice in these heavily pretreated patients is to continue trastuzumab in combination with chemotherapy. As such, the effect of dual blockade and trastuzumab plus chemotherapy in the HER2-enriched cohort will be evaluated in this study~~

Reason for Change

Section 3.1.3 Analysis of the biomarker was updated to emphasize immunomodulation

Original Text

This study will have tumor biopsies taken at screening (pre-treatment biopsy) and at disease progression (progression biopsy), to analyze candidate biomarkers defined for each of the 4 primary mechanisms associated with impacting response to chemotherapy (see Section 1.2.3). The primary endpoint will evaluate changes in the candidate biomarkers measured in the progression biopsy compared to the pre-treatment biopsy.

Analysis of these candidate biomarkers in pre-treatment tumor tissue and at disease progression may provide key information on modulation, as an effect of treatment, or persistence of the breast molecular subtype through the course of the history of the disease.

The site of the pre-treatment biopsy and progression biopsy should remain the same if possible. CNS and bone biopsies are excluded organs.

[redacted] Subpopulations of natural killer cells, monocytes/macrophages, and T-cells, as resting and activated phenotypes, will be evaluated as well as levels of cytokines and chemokines associated with immune responses.

Amended Text

This study will have tumor biopsies taken at screening (pre-treatment biopsy) and at disease progression (progression biopsy) to analyze ~~candidate~~biomarkers **associated with immunomodulation potentially** ~~defined for each of the 4 primary mechanisms associated~~**connected** ~~with~~**to an impact on the**~~impacting~~ response to chemotherapy (see Section 1.2.3). The primary endpoint will evaluate changes in the**se** ~~candidate~~ biomarkers measured in the progression biopsy compared to the pre-treatment biopsy.

Analysis of these candidate biomarkers in pre-treatment tumor tissue and at disease progression may provide indicative information on immunomodulation, as an effect of treatment.

~~Analysis of these candidate biomarkers in pre-treatment tumor tissue and at disease progression may provide key information on modulation, as an effect of treatment, or persistence of the breast molecular subtype through the course of the history of the disease.~~

The site of the pre-treatment biopsy and progression biopsy should remain the same if possible. CNS and bone biopsies are excluded organs.

[redacted] ~~Subpopulations of natural killer cells, monocytes/macrophages, and T-cells, as resting and activated phenotypes, will be evaluated as well as levels of cytokines and chemokines associated with immune responses.~~

Reason for Change

Section 4.1.1 Number of current enrollment provided. Novartis will stop enrollment completely when study termination proposal agreement is received from HA. The projection on the analysis of the originally planned number of patient was deleted due to early study termination.

Original Text

The study will analyze a minimum of 150 evaluable subjects, 50 in each arm. To achieve 150 evaluable subjects, it is estimated that approximately 225 subjects will be enrolled (75 in each treatment arm) based on the assumption that approximately 85% of subjects will discontinue study treatment due to disease progression and of these, 80% will have evaluable paired tumor biopsies.

See Section 9.2.1 for sample size assumptions.

Amended Text

Since the initiation of this trial, the enrollment has been poor due to lack of interest by investigators and patients. Therefore, future enrolment will be halted and the study will be terminated early. Up to 31 Jul 2016, 29 patients have been enrolled. ~~The study will analyze a minimum of 150 evaluable subjects, 50 in each arm. To achieve 150 evaluable subjects, it is estimated that approximately 225 subjects will be enrolled (75 in each treatment arm) based on the assumption that approximately 85% of subjects will discontinue study treatment due to disease progression and of these, 80% will have evaluable paired tumor biopsies.~~

~~See Section 9.2.1 for sample size assumptions.~~

Reason for Change

Section 4.2.1 Withdraw of consent was added for study discontinuation definition**.** Follow up time was re-defined

Original Text

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry defined in Section 5.9 or for hematologic and other non-hematologic toxicity. In addition, study treatment may be permanently discontinued for any of the following reasons:

All subjects who discontinues from study treatment will have safety and efficacy assessments performed as specified in the Time and Events table (Table 9) and results documented in the eCRF.

After discontinuation of the study treatment for any reason, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected.

If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.). All details of post-study anticancer treatments including start dates, stop dates, reason for ending treatment, and dates of documented disease progression (radiologic and/or clinical), will be captured in the relevant sections of the eCRF until death or end of study.

All subjects who discontinue from study treatment without disease progression will be followed for progression according to the protocol schedule (Table 9) until new anticancer therapy is initiated, progression or death is documented, or study closes.

Survival follow-up will continue until all criteria below are met:

- 75% of the subjects have died
- 100% of subjects have completed study treatment;
- all subjects who go onto first next line therapy have completed first next line therapy.

At such time, the study will be closed for further follow-up and collection of all post-study information will cease. .

Amended Text

Subjects will receive study treatment until disease progression, death**, withdrawal of consent or any other reasons mentioned in this section, including** ~~or~~ unacceptable

adverse event **(as well as**~~including~~ meeting stopping criteria for liver chemistry defined in Section 5.9 or for hematologic and other non-hematologic toxicity**)**.

~~In addition, s~~**S**tudy treatment may be permanently discontinued for any of the following reasons:

All subjects who discontinue from study treatment **due to an AE or any other reasons other than disease progression** will have safety and efficacy assessments performed **until disease progression, new anticancer therapy, death, withdrawal or until the end of study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression)** as specified in the Time and Events table (Table 9) and results documented in the eCRF.

In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- **All patients have died or discontinued from the study**
- **Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study**

- **At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.**

~~After discontinuation of the study treatment for any reason, a subject will be followed for survival at approximately 12-week intervals until death or end of study. Information on subsequent anti-cancer therapy(ies), start and stop dates of administrations of anti-cancer therapy, and dates of documented disease progression will also be collected.~~

~~If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.).~~

~~All details of post-study anticancer treatments including start dates, stop dates, reason for ending treatment, and dates of documented disease progression (radiologic and/or clinical), will be captured in the relevant sections of the eCRF until death or end of study.~~

~~All subjects who discontinue from study treatment without disease progression will be followed for progression according to the protocol schedule (Table 9) until new anticancer therapy is initiated, progression or death is documented, or study closes.~~

~~Survival follow-up will continue until all criteria below are met:~~

- ~~75% of the subjects have died~~
- ~~100% of subjects have completed study treatment;~~
- ~~all subjects who go onto first next line therapy have completed first next line therapy.~~

~~At such time, the study will be closed for further follow-up and collection of all post-study information will cease.~~

Reason for Change

Section 4.2.2 Minor editorial changes to clarify the timing of lost to follow up

Original Text

If any of the trial subjects are lost to follow up, contact will initially be attempted through the trial research nurse and the lead investigator at each centre.

Amended Text

If any of the trial subjects are lost to follow-up **prior to subject completion**, contact will initially be attempted through the trial research nurse and the lead investigator at each centre.

Reason for Change

Section 4.2.3 Subject Completion: Follow-up time was re-defined

Original Text

A subject will be considered to have completed the study if the subject dies during the study treatment or follow-up period. Document the cause of death in the eCRF.

A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated.

Data collection will continue until a subject has completed or discontinued the study. Collection of follow-up data will continue until

- 75% of the subjects have died (or at most 25% subjects are censored)

- 100% of subjects have completed study treatment;
- all subjects who go onto first next line therapy have completed first next line therapy.

Amended Text

A subject will be considered to have completed the study if the subject **presents with disease progression, starts a new anti-cancer therapy,** dies **or withdraws from the study, starts a new anti-cancer therapy or the study ends whichever comes first** ~~during the study treatment or follow-up period~~. Document the cause of ~~death~~ **completion** in the eCRF.

A subject will be considered to have withdrawn from the study if the subject has not ~~died~~ **experienced disease progression** and is lost to follow-up, has withdrawn consent, **or has withdrawn** at the investigator's discretion. ~~is no longer being followed or if the study is closed/terminated.~~ **All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal of consent or any other reasons mentioned in section 4.2.1.**
In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study (defined as all subjects having completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons other than disease progression), no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subject will be followed-up for safety and efficacy assessments until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:
- **All patients have died or discontinued from the study**
- **Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study**

- **At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.**

Data collection will continue until a subject has completed or discontinued the study.

~~Collection of follow-up data will continue until~~

- ~~75% of the subjects have died (or at most 25% subjects are censored)~~
- ~~100% of subjects have completed study treatment;~~
- ~~all subjects who go onto first next line therapy have completed first next line therapy.~~

Reason for Change

Section 4.3 Requirement of number of evaluable patient was removed for screen failures

Original Text

When a treatment arm(s) has enrolled the required 50 evaluable subjects, subjects who signed consent after receipt of the notification letter and are newly screened with the molecular subtype of the fully enrolled arm will be considered screen failures.

Amended Text

~~When a treatment arm(s) has enrolled the required 50 evaluable subjects, subjects who signed consent after receipt of the notification letter and are newly screened with the molecular subtype of the fully enrolled arm will be considered screen failures.~~

Reason for Change

Section 5.1.1 Commercial lapatinib is allowed to be used

Original Text

Lapatinib is supplied as 250-mg orange tablets that are oval, biconvex, and orange film-coated with 1 side plain and the opposite side debossed with FG HLS.

Amended Text

Commercially packed supplies or non-commercial ~~Lapatinib~~ lapatinib is supplied as 250-mg orange tablets that are oval, biconvex, and orange film-coated with 1 side plain and the opposite side debossed with FG HLS.

Reason for Change

Section 5.4 Requirement of number of evaluable patient was removed for treatment assignment

Original Text
After an arm enrolled at least 50 evaluable subjects, that arm will be closed for further enrolled. It is likely that Non-HER2-enriched Dual blockade arm will accrue 50 evaluable subjects before the HER2-enriched arms. If the Non-HER2-enriched Dual blockade arm is closed to further enrollment, subjects who sign consent after receipt of written notification and have a pre-treatment biopsy that is Non-HER2-enriched will be considered as screen failures (Section 4.3).

Amended Text
~~After an arm enrolled at least 50 evaluable subjects, that arm will be closed for further enrolled. It is likely that Non-HER2-enriched Dual blockade arm will accrue 50 evaluable subjects before the HER2-enriched arms. If the Non-HER2-enriched Dual blockade arm is closed to further enrollment, subjects who sign consent after receipt of written notification and have a pre-treatment biopsy that is Non-HER2-enriched will be considered as screen failures (Section 4.3).~~

Reason for Change

Section 5.8 Death was added to define the end of study treatment administration

Original Text

Study treatment will be administered until disease progression or discontinuation of study treatment due to unacceptable toxicity or other reasons (i.e., consent withdrawal, non-compliance).

Amended Text

Study treatment will be administered until disease progression **or death** or discontinuation of study treatment due to unacceptable toxicity or other reasons (i.e. consent withdrawal, non-compliance).

Reason for Change

Section 5.9.1.1 Survival and progression follow-up were removed after discontinuation from the study due to hepatobiliary events

Original Text

- Withdraw the subject from the study after completion of the liver chemistry monitoring as described below (unless further safety follow up is required or GSK Medical Governance approval of drug restart is granted, as described in Section 5.9.2).

  For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment

- Do not restart investigational product unless written approval for drug restart is granted by GSK Medical Governance (details for restarting investigational product are described in Section 5.9.2), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 5.9).

Amended Text

- Withdraw the subject from the study after completion of the liver chemistry monitoring as described below (unless further safety follow-up is required or ~~GSK Medical Governance~~ approval of drug restart is granted, as described in Section 5.9.2).

  ~~For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment~~

- Do not restart ~~investigational product~~ **study treatment** unless written approval for drug restart is granted ~~by GSK Medical Governance~~ (details for restarting ~~investigational product~~ **study treatment** are described in Section 5.9.2), whereupon the subject continues in the study after completion of the liver chemistry monitoring described in Section 5.9).

Reason for Change

Section 6.3 Overall survival and progression follow up were removed for subjects who discontinued from study. For subjects who discontinue for any other reasons other than progression, new anti-cancer therapy will be recorded during the follow-up period until subject completion.

Original Text

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment. Refer to Section 4.2.3 for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinuing study treatment.

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) anticancer therapy at the discretion of the treating physician. Every effort should be made to complete the required withdrawal and follow-up evaluations prior to initiating further anticancer therapy or dosing of an investigational agent (see Table 9) or follow-up assessments and procedures).

New anticancer therapy should be documented on the eCRF with generic drug name, start and stop dates, regimen sequence, type of therapy, number of cycles/dose, dose units, date of disease progression (if applicable), and reason for discontinuing post-study treatment.

Subjects will be followed for survival even if other assessments are not performed.

Amended Text

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition~~whether or not GSK is providing specific post-study treatment. Refer to Section for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinuing study treatment.~~

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) anticancer therapy at the discretion of the treating physician. Every effort should be made to complete the ~~required withdrawal~~ **end of study** ~~and follow-up~~ evaluations prior to initiating further anticancer therapy or dosing of an investigational agent (see Table 9~~) or follow-up assessments and procedures)~~.

For subjects who discontinue for any other reasons other than progression, new anti-cancer therapy will be recorded during the follow-up period until subject completion. New anticancer therapy should be documented on the eCRF with generic drug name, start and stop dates, regimen sequence, type of therapy, number of cycles/dose, dose units ~~date of disease progression (if applicable),~~ and reason for discontinuing post-study treatment.

~~Subjects will be followed for survival even if other assessments are not performed.~~

Reason for Change

Section 7 Time and Events are updated. Overall survival follow-up and new anticancer therapy were removed for subjects who stopped study treatment due to progression. Progression follow-up was kept for subjects who discontinued treatment for any other reasons than progression.

Original Text

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Procedures								
Informed Consent		X						
Inclusion / exclusion		X						

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Demographics	Include birth year, race, ethnicity, and gender	X						
Surgical history		X						
Anti-cancer therapies		X[1]						X[2]
Past /current med conditions		X	X					
Translational Sample Collection								
Tumor Biopsy	[redacted] refer to Study Procedures Manual for biopsy sample collection, storage, and shipment procedures	X					X[3]	
Archived/stored tumor tissue collection	Tumor tissue block or 15-20 unstained slides required	X						
[redacted]								

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Efficacy Assessments								
Disease Assessment[4]	Target and nontarget lesions should be assessed using RECIST 1.1 within 28 days prior to randomization; assessments are conducted every 9 weeks until 54 weeks then every 24 weeks thereafter.	X			X		X[5]	X[6]
Bone Scan[7]	Baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated. For subjects with bone disease at baseline, a bone scan is required every 18 weeks and at disease progression until Week 54 and then every 24 weeks or as clinically indicated	X						
Post study treatment efficacy	Record dates of documented disease progression							X
Survival								X
Safety Assessments								
Concurrent meds		X	X	X				

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Physical exam		X	X	X			X	
Vital signs	Temperature, blood pressure and heart rate	X	X	X				
Weight & height	Height - screening only	X	X	X				
ECOG PS		X	X	X			X	
AE/toxicity	Subjects will be monitored every 6 weeks or at any contact with the subject during the study phases		X	X			X	X[8]
ECHO or MUGA scan[9]	The same method of evaluation should be used for a subject throughout study duration	X				X	X	
12-lead ECG		X				X	X	
Laboratory Assessments[10]								
Hematology	Includes hemoglobin, hematocrit, red blood cell count, white blood cell count with absolute neutrophil count or differential, and platelet count	X	X	X			X	
Serum chemistry[11]	Includes sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, aspartate aminotransferase, alanine aminotransferase,	X	X	X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	alkaline phosphatase, total bilirubin, and albumin. magnesium							
Serum pregnancy test	Required for all women of childbearing potential; to be performed within 7 days prior to start of first dose of study treatment	X						

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Study Treatment Assessments								
Dispense lapatinib	A supply of lapatinib will be dispensed to subject with instructions for administration		X					
Trastuzumab administration	Weekly schedule is permitted in combination with chemotherapy. Window for dose administration is ± 3 days.		X	X				
Chemotherapy administration[12]	Dose and schedule as prescribed by the investigator		X					
Endocrine therapy with AI administration[13]	Dose and schedule as prescribed by the investigator in subjects with hormone receptor positive disease		X					
Study drug compliance	A record of the number of tablets dispensed to and returned by each subject must be maintained			X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	Study Treatment Discontinuation	Follow-Up Every 12 Weeks
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Quality of Life Assessments								
FACT-B questionnaire & MAF questionnaire	On Day 1 collected at start of study treatment. Subsequent assessments in treatment phase include Week 3, week 6, and Week 12.		X	X		X	X	

1. Prior therapies (screening visit only): include administration start and stop dates (month, year); date of radiographic confirmed progression.
2. Post study therapies: After study treatment discontinuation follow subject for start and stop dates of all anti-cancer therapies administered.
3. Window for progression biopsy is +14 days from date of progression and prior to start of new anti-cancer therapy. Biopsy of metastatic tumor site only in subjects who discontinue study treatment due to disease progression.
4. Use the same method of measurement for target and nontarget lesions at all time points.
5. If the last radiographic assessment was obtained less than 9 weeks from study treatment discontinuation, radiographic assessments do not need to be repeated.
6. Subjects who discontinue study treatment for reasons other than progression will have disease assessments done every 9 weeks until Week 54, then every 24 weeks thereafter until unequivocal progression, initiation of new anticancer therapy, or death
7. All bone scan abnormalities that may indicate metastases must be evaluated by X-ray (e.g., plain film), computed tomography(CT), or magnetic resonance imaging to confirm and/or quantify malignant lesions.
8. Monitor all AEs/Serious AEs that are ongoing until resolution or stabilization of the event
9. Additional ECHO/ MUGA scans should be performed when clinically indicated.
10. At the pre-dose assessment on Day 1, all laboratory results will be reviewed by the investigator. Any results outside of the normal range will be repeated (prior to the first dose) at the discretion of the investigator
11. Refer to Protocol Appendix 4 for further details
12. Chemotherapy will be administered throughout the study treatment phase based on the schedule chosen by investigator.
13. Endocrine therapy with AIs will be administered throughout the study treatment phase based on the schedule chosen by investigator.

[redacted]

15. Abbreviations: ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; MUGA, multigated acquisition scan.

Amended Text

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Procedures								
Informed Consent		X						
Inclusion / exclusion		X						
Demographics	Include birth year, race, ethnicity, and gender	X						
Surgical history		X						
Anti-cancer therapies		X[1]						~~X~~[2]**X**[14]
Past /current med conditions		X	X					
Translational Sample Collection								
Tumor Biopsy	[redacted] refer to Study Procedures Manual for biopsy sample collection, storage, and	X					~~X~~[3]**X**[2]	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	shipment procedures							
Archived/stored tumor tissue collection	Tumor tissue block or 15-20 unstained slides required	X						
[redacted]								
[redacted]								
Efficacy Assessments								
Disease ~~Assessment[4]~~**Assessment[3]**	Target and nontarget lesions should be assessed using RECIST 1.1 within 28 days prior to randomization; assessments are conducted every 9 weeks	X			X		~~X[5]~~**X[4]**	X[5~~6~~]

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	until 54 weeks then every 24 weeks thereafter.							
Bone ~~Scan[7]~~**Scan[6]**	Baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated. For subjects with bone disease at baseline, a bone scan is required every 18 weeks and at disease progression until Week 54 and then every 24 weeks or as clinically indicated	X						
Post study treatment efficacy **for subjects who discontinued study treatment for reasons other than disease progression**	Record dates of documented disease progression							X
~~Survival~~								~~X~~
Safety Assessments								

STUDY PHASE		**PRE-TREATMENT**		**TREATMENT**			**POST-TREATMENT**	
VISIT		**Screen**	**Day 1**	**Every 3 weeks**	**Every 9 Weeks**	**Every 12 Weeks**	**At Study Treatment Discontinuation**	**Follow-Up Every 12 Weeks until subject completion**
VISIT WINDOW (±Days)				**± 7**	**± 7**	**-7**		**±30**
Concurrent meds		X	X	X			**X**	
Physical exam		X	X	X			X	
Vital signs	Temperature, blood pressure and heart rate	X	X	X			**X**	
Weight & height	Height - screening only	X	X	X				
ECOG PS		X	X	X			X	
AE/toxicity	Subjects will be monitored every 6 weeks or at any contact with the subject during the study phases		X	X			X[7]	~~X~~[8]**X**[7]
ECHO or MUGA ~~scan~~[9]**scan**[8]	The same method of evaluation should be used for a subject throughout study duration	X				X	X	
12-lead ECG		X				X	X	
Laboratory ~~Assessments~~[10]Assessments[9]								
Hematology	Includes hemoglobin, hematocrit, red blood cell count, white blood cell count with absolute neutrophil count or differential,	X	X	X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
	and platelet count							
Serum ~~chemistry[11]~~**chemistry[10]**	Includes sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin. magnesium	X	X	X			X	
Serum pregnancy test	Required for all women of childbearing potential; to be performed within 7 days prior to start of first dose of study treatment	X						

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
Study Treatment Assessments								
Dispense lapatinib	A supply of lapatinib will be dispensed to subject with instructions for administration		X					
Trastuzumab administration	Weekly schedule is permitted in combination with chemotherapy. Window for dose administration is ± 3 days.		X	X				
Chemotherapy ~~administration[12]~~**administration[11]**	Dose and schedule as prescribed by the investigator		X					
Endocrine therapy with AI ~~administration[13]~~**administration[12]**	Dose and schedule as prescribed by the investigator in subjects with hormone receptor positive disease		X					
Study drug compliance	A record of the number of tablets dispensed to and returned by each subject must be maintained			X			X	

STUDY PHASE		PRE-TREATMENT		TREATMENT			POST-TREATMENT	
VISIT		Screen	Day 1	Every 3 weeks	Every 9 Weeks	Every 12 Weeks	At Study Treatment Discontinuation	Follow-Up Every 12 Weeks until subject completion
VISIT WINDOW (±Days)				± 7	± 7	-7		±30
~~Quality of Life Assessments~~								
~~FACT-B questionnaire & MAF questionnaire~~	~~On Day 1 collected at start of study treatment. Subsequent assessments in treatment phase include Week 3, week 6, and Week 12.~~		~~X~~	~~X~~		~~X~~	~~X~~	

1. Prior therapies (screening visit only): include administration start and stop dates (month, year); date of radiographic confirmed progression.
2. ~~Post study therapies: After study treatment discontinuation follow subject for start and stop dates of all anti-cancer therapies administered.~~
3. Window for progression biopsy is +14 days from date of progression and prior to start of new anti-cancer therapy. Biopsy of metastatic tumor site only in subjects who discontinue study treatment due to disease progression.
4. Use the same method of measurement for target and nontarget lesions at all time points.
5. If the last radiographic assessment was obtained less than 9 weeks from study treatment discontinuation, radiographic assessments do not need to be repeated.
6. Subjects who discontinue study treatment for reasons other than progression **(e.g. due to an AE)** will have disease assessments done every 9 weeks until Week 54, then every 24 weeks thereafter until unequivocal progression, initiation of new anticancer therapy, **death, withdrawal of consent,** ~~or death~~**or end of study. At the end of study, if the last radiographic assessment was obtained less than 9 weeks earlier, radiographic assessment does not need to be repeated.**
7. All bone scan abnormalities that may indicate metastases must be evaluated by X-ray (e.g., plain film), computed tomography (CT), or magnetic resonance imaging to confirm and/or quantify malignant lesions.
8. **Safety monitoring will be performed until 30 days after the last dose for subjects who discontinued due to progression. Safety monitoring will continue for subjects who stopped study treatment for reasons other than disease progression until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.** Monitor all AEs/Serious AEs that are ongoing until resolution or stabilization of the event.
9. Additional ECHO/ MUGA scans should be performed when clinically indicated.

10. At the pre-dose assessment on Day 1, all laboratory results will be reviewed by the investigator. Any results outside of the normal range will be repeated (prior to the first dose) at the discretion of the investigator
11. Refer to Protocol Appendix 4 for further details
12. Chemotherapy will be administered throughout the study treatment phase based on the schedule chosen by investigator.
13. Endocrine therapy with AIs will be administered throughout the study treatment phase based on the schedule chosen by investigator.

[redacted]

15. **For subjects who discontinue for any other reasons other than progression, new anti-cancer therapy will be recorded during the follow-up period until subject completion**.

Abbreviations: ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; MUGA, multigated acquisition scan.

Reason for Change

Section 7.3.1 Efficacy endpoints was updated to remove OS, and PFS on first next-line and subsequent line of anti-cancer therapies and to remove the wider assessment of the biomarkers

Original Text
The primary efficacy endpoint of this study is the change in biomarkers associated with human epidermal growth factor (HER) family, immunomodulation, apoptosis, and ABC transporters which is defined as change in expression levels of biomarkers as measured in tissue from the disease progression tumor biopsy, compared with expression levels of these markers as measured in the pre-treatment tumor biopsy.

The secondary efficacy endpoints of this study are:

- OS defined as the interval of time between randomization and death due to any cause; investigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months
- PFS on all subsequent lines of anti-cancer therapies defined as the interval of time between start of next-line anticancer therapy and disease progression or discontinuation of that next-line therapy for any cause
- Determine if 1) an on-treatment change or 2) change at disease progression in biomarker correlates with PFS, PFS-NL or OS

[redacted]

Amended Text
The primary efficacy endpoint of this study is the change in biomarkers associated with ~~human epidermal growth factor (HER) family,~~ immunomodulation~~, apoptosis, and ABC~~

~~transporters~~ which is defined as change in expression levels of biomarkers as measured in tissue from the disease progression tumor biopsy , compared with expression levels ~~of these markers~~ as measured in the pre-treatment tumor biopsy.

The secondary efficacy endpoints of this study are:

~~OS defined as the interval of time between randomization and death due to any cause;~~ **I~~i~~**nvestigator-assessed PFS defined as the interval of time between randomization and disease progression or death due to any cause; investigator-assessed ORR defined as percentage of subjects with a CR or PR; and CBR defined as percentage of subjects with a CR, PR, or SD for at least 6 months.

- ~~PFS on all subsequent lines of anti-cancer therapies defined as the interval of time between start of next-line anticancer therapy and disease progression or discontinuation of that next-line therapy for any cause~~
- ~~Determine if 1) an on-treatment change or 2) change at disease progression in biomarker correlates with PFS, PFS-NL or OS~~

[redacted]

Reason for Change

Section 7.3.2 Minor editorial change to clarify the bone scans timeline
Original Text

For subjects with bone disease at baseline, a bone scan is required every 18 weeks and at disease progression until Week 54 and then every 24 weeks or as clinically indicated.

Amended Text

For subjects with bone disease at baseline, a bone scan is required every 18 weeks **until Week 54 and then every 24 weeks or as clinically indicated** and at disease progression~~until Week 54 and then every 24 weeks or as clinically indicated.~~

Reason for Change

Section 7.3.2.1 Removal of reference to Image Acquistion Guidelines as not applicable for this study.

Original Text

Contrast agents must be used in accordance with the Image Acquisition Guidelines.

Amended Text

~~Contrast agents must be used in accordance with the Image Acquisition Guidelines.~~

Reason for Change

Section 7.3.2.3 updated to follow up for disease progression only, not survival. Efficacy assessment update is the same as in **Section 7.**

Original Text

Refer to Section 4.2 Permanent Discontinuation from Study Treatment and Time and Events Schedule (Table 9) for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinuing from study treatment

Efficacy Assessments at Follow-up

All subjects who discontinue study treatment will be followed for survival and any subsequent anticancer therapy including start date, stop date, reason for stopping therapy, and date of progression, if applicable, every 12 weeks until death or end of study. Clinical or radiographic disease progression can be used in survival follow up.

Amended Text

Refer to Section 4.2 Permanent Discontinuation from Study Treatment and Time and Events Schedule (Table 9) for follow-up assessment of subjects who are to be followed up for disease progression ~~and/or survival~~ after permanently discontinuing ~~from~~ study treatment **for any reasons other than disease progression.**

Efficacy Assessments ~~at Follow-up~~for subjects who discontinued study treatment for reasons other than progression

~~All subjects who discontinue study treatment will be followed for survival and any subsequent anticancer therapy including start date, stop date, reason for stopping therapy, and date of progression, if applicable, every 12 weeks until death or end of study. Clinical or radiographic disease progression can be used in survival follow up.~~

Subjects who discontinue study treatment for reasons other than progression will have disease assessments done every 9 weeks until Week 54, then every 24 weeks thereafter until unequivocal progression, initiation of new anticancer therapy, death, withdrawal of consent or end of study (defined in section 10.5).

Reason for Change

Section 7.4.3 Removed the language about AE (related to study drug) follow-up after 30 days.

Original Text

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.4.5.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any adverse event that they believe possibly related to study treatment.

Amended Text

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) **or** study treatment ~~or GSK concomitant medication~~ must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported ~~to GSK~~ within 24 hours, as indicated in Section 7.4.5.

~~After discontinuation of~~ study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. ~~At any time after 30 days the investigator may report any adverse event that they believe possibly related to study treatment.~~

Reason for Change

Section 7.6 The analyses will be focused on biomarkers associated with immuno-modulation

Original Text

Translational research will be performed on tissue and blood samples collected during the course of the trial to evaluate or identify factors or profiles that correlate with measures of response to study treatment or response to subsequent anti-cancer treatments. Analyses to identify biomarker profiles correlating with other factors or disease characteristics that include but are not be limited to breast cancer histological grade and molecular subtype may also be performed.

Comparative examination of pre-dosing tumor-derived or blood-derived profiles may uncover known or novel candidate biomarkers/profiles that could be used to predict

response to study treatment, subsequent anti-cancer treatment, or provide new insights into breast cancer or medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of study treatment.

All samples may be retained for a maximum of 15 years after the last subject completes the trial.

Candidate biomarkers, novel biomarkers, profiles, and subsequently discovered biomarkers/profiles of biological response associated with breast cancer or medically related conditions and/or the action of study treatment may be identified by application of:

- DNA/gene and protein analysis of tumor tissue
- Circulating/systemic biomarkers
    - cytokines and angiogenic factors (CAF) analysis of blood sample
    - peripheral blood mononuclear cells (PBMC) analysis of whole blood
    - Cell-free DNA (cfDNA)
- RNA transcriptome analysis of blood and tumor tissue samples
- Measurement of the levels of a subset of RNA species on blood and tumor tissue samples
- Proteome analysis of blood sample and tumor tissue samples

DNA research on tumor tissue or circulating cfDNA may include methods that determine the prescence of known mutations in specific genes (e.g., PIK3CA, TP53, and PTEN) or approaches that sequence the whole genome or whole exome of tumor-derived DNA.

RNA research and/or RNA expression research of a subset of RNA species may be included as relevant for the study. RNA expression studies may be conducted using methods that provide whole transcriptome analysis, quantitative measurement of defined RNA species, and/or the application of emerging technologies that can facilitate the simultaneous measurement of the abundances of RNA species resulting in a RNA expression profile for the blood samples.

Amended Text

Translational research will be performed on tissue and blood samples collected during the course of the trial to evaluate **if immune markers are modulated by the treatment. These analyses will highlight eventual changes in expression levels and/or presence (and localization) of immunological cells/markers in relation to treatment.** ~~or identify~~

~~factors or profiles that correlate with measures of response to study treatment or response to subsequent anti-cancer treatments.~~

Analyses to identify biomarker**s or** profiles correlating with **response,** ~~other factors~~ or disease characteristics that include but are not be limited to breast cancer histological grade and molecular subtype may also be performed **if sample numbers allow.**

~~Comparative examination of pre-dosing tumor-derived or blood-derived profiles may uncover known or novel candidate biomarkers/profiles that could be used to predict response to study treatment , subsequent anti-cancer treatment, or provide new insights into breast cancer or medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of study treatment.~~

All samples may be retained for a maximum of 15 years after the last subject completes the trial.

~~Candidate biomarkers, novel biomarkers, profiles, and subsequently discovered biomarkers/profiles of biological response associated with breast cancer or medically related conditions and/or the action of study treatment may be identified by application of:~~

- ~~DNA/gene and protein analysis of tumor tissue~~
- ~~Circulating/systemic biomarkers~~
    - ~~cytokines and angiogenic factors (CAF) analysis of blood sample~~
    - ~~peripheral blood mononuclear cells (PBMC) analysis of whole blood~~
    - ~~Cell-free DNA (cfDNA)~~
- ~~RNA transcriptome analysis of blood and tumor tissue samples~~
- ~~Measurement of the levels of a subset of RNA species on blood and tumor tissue samples~~
- ~~Proteome analysis of blood sample and tumor tissue samples~~

~~DNA research on tumor tissue or circulating cfDNA may include methods that determine the prescence of known mutations in specific genes (e.g., PIK3CA, TP53, and PTEN) or approaches that sequence the whole genome or whole exome of tumor-derived DNA.~~

~~RNA research and/or RNA expression research of a subset of RNA species may be included as relevant for the study. RNA expression studies may be conducted using methods that provide whole transcriptome analysis, quantitative measurement of defined RNA species, and/or the application of emerging technologies that can facilitate the~~

~~simultaneous measurement of the abundances of RNA species resulting in a RNA expression profile for the blood samples.~~

Reason for Change

Section 7.6.1 Tumor biomarker analysis was clarified

Original Text

In order to further characterize the subject population, DNA, RNA, and protein biomarkers (e.g., tumor/somatic gene mutations, expression of genes and proteins) and/or profiles related to breast cancer and the activity of the study treatment will be assessed in archival/stored tissue (original diagnosis or a recent biopsy), fresh pre-treatment tumor biopsy and in tumor tissue obtained at disease progression.

Additional analyses may include the evaluation of histological features to include but are not limited to the enumeration of cell type populations such as lymphocytes.

For the archival stored tissue, a formalin-fixed, paraffin-embedded tumor tissue block taken at a metastatic site or obtained at the time of original primary cancer diagnosis (biopsy or from definitive surgery) is required to be submitted to the central laboratory. Alternatively, sites may send 15-20 freshly sectioned, unstained slides containing 5-micron thick sections.

Amended Text

Markers of the immune microenvironment will be analyzed in pre-treatment tumor biopsies and in paired tumor tissue obtained at disease progression. These analyses will include tumor infiltrating lymphocytes (TILs) and a seleted immune mRNA gene expression panel (e.g. Nanostring platform), including mRNA markers for specific immune cell populations (e.g. CD8 positive T-cells, B-cells, Tregs). Gene expression levels in the disease progression biopsy will be compared to the baseline biopsy to assess how the treatments affect the immune response at the level of the tumor.

In addition, immunological cells (and protein markers) may be investigated; such analyses may include, but are not limited to PD-L1, CD8 protein expression levels as determinded by immunohistochemistry, Treg cells, macrophages, and expression of additional checkpoint molecules, in the context of tumor and tumor associated stroma.

~~In order to further characterize the subject population, DNA, RNA, and protein biomarkers (e.g., tumor/somatic gene mutations, expression of genes and proteins) and/or profiles related to breast cancer and the activity of the study treatment will be assessed in archival/stored tissue (original diagnosis or a recent biopsy), fresh pre-treatment tumor biopsy and in tumor tissue obtained at disease progression.~~

~~Additional analyses may include the evaluation of histological features to include but are not limited to the enumeration of cell type populations such as lymphocytes.~~

Reason for Change

[redacted]

[redacted]

Section 8 Data Management is modified to be consistent with the Novartis Data Management process

Orignial Text

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives.

For this study subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to the sponsor (or designee) and be combined with data provided from other sources in a validated data system. The electronic data capture system InForm will be used to collect all of the subject information by the investigator.

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g. resolving errors and

inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and a custom drug dictionary. eCRFs (including queries and audit trails) will be retained by the sponsor, and copies will be sent to the investigator to maintain as the investigator copy.

Amended Text

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives.

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system. The electronic data capture system InForm will be used to collect all of the subject information by the investigator.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Reason for Change

Section 9.1 HER2 family, apoptosis, and adenosine triphosphate binding cassette (ABC) were removed from the hypothesis

Original Text

The primary objective of this study is to determine if trastuzumab in combination with lapatinib or chemotherapy changes expression of biomarkers associated with HER family of receptor and ligands, immunomodulation, apoptosis, and ABC transporters. The primary endpoint will be analyzed by treatment arm with a descriptive intent only. The study is not powered to detect differences between the treatment arms and as such no formal treatment arm comparisons will be made.

Amended Text

The primary objective of this study is to determine if trastuzumab in combination with lapatinib or chemotherapy changes expression of biomarkers associated with ~~HER family of receptor and ligands,~~ immunomodulation~~, apoptosis, and ABC transporters.~~ The primary endpoint will be analyzed by treatment arm with a descriptive intent only. The study is not powered to detect differences between the treatment arms and as such no formal treatment arm comparisons will be made.

Reason for Change

Section 9.2.1 Sample size was removed and added the current number of enrolled patients.

Original Text

A pre-treatment biopsyand a biopsy at disease progression will provide the samples for biomarker analysis.

A multigene platform such as Nanostring, microarray, or RNA-seq may be utilized to assess gene expression changes. Subsets of genes of interest have been *a priori* defined and changes from baseline of these genes will be assessed. To address the issue of multiple comparisons, metagene analysis, false discovery rate (FDR) or other adjustments will be implemented within each group of genes, as appropriate.

Sample size requirements for detection of global on-treatment changes in biomarker expression in a multigene platform such as a microarray require many assumptions about structure of the data. Table 14 shows sample size calculations using the approach of Shao and Tseng [Shao, 2007]. This approach assumes 10,000 hypothesis tests with a range of *m* true positive changes, an effect size=1 (δ=1, based on $\log_2$ expression, reflecting a 2 fold change in gene expression), 5% FDR, and detection of 80% of true positives with 80% probability. In addition, a general correlation of 0.1 among all genes is assumed, and a range of possible block-wise correlations in null and alternative genes, as indicated in Table 14 is considered.

Table 17 Sample size estimates for a range of data structures

	Number true positives (*m*)		
Correlation	20	200	1000
0.2	48	37	28
0.5	49	38	30
0.8	51	40	31

Based on this assessment, a 1:1 randomization scheme for HER2-enriched cohort and enrolment into treatment arm C for Non-HER2-enriched cohort will be used with approximately 225 subjects to achieve 50 evaluable subjects in each arm. This sample size ensures adequate power for global on-treatment changes in biomarker expression as well as for individual genes, metagenes, or specific subsets of genes of interest. For individual genes or metagenes, the probability of detecting statistically significant gene expression differences between pre-treatment and progression samples, with an effect size of 1 and α=0.05, and a sample size of 50, is >95%. Adjustments for multiple comparisons will be made for groups of individual genes, pre specified in the analysis

plan. For example, HER family of receptors and ligands may form a group of genes, with a total of 15 genes in the group (HER Receptors: EGFR, HER2, HER3, HER4; HER Ligands: AR, BTC, EGF, EPGN, EPR, HBEGF, TGFα, NRG1, NRG2, NRG3, and NRG4). In this example, a total of 15 genes would be assessed for on treatment changes in expression, with each comparison having power of >95% (α=0.05, δ=1). In order to adjust for multiple comparisons, FDR at a level of 0.05 would be recommended. Smaller prespecified groups of genes (5 genes or less) may be adjusted using the Bonferroni adjustment.

This sample size will also allow for a sufficient number of subjects to estimate a key secondary endpoint, PFS on next line anti-cancer therapy (PFS-NL). Based on EGF104900, approximately 70% of subjects are expected to continue on next line anti-cancer therapy, thus data from approximately 35 subjects per arm may be available for PFS-NL.

Amended Text

This is a purely descriptive study. Due to difficulty in enrolling subjects into this trial, future enrolment will be halted and the study will be terminated early. Up to 31 Jul 2016, 29 patients have been enrolled.

A pre-treatment biopsy and a biopsy at disease progression will provide the samples for biomarker analysis.

~~A multigene platform such as Nanostring, microarray, or RNA-seq may be utilized to assess gene expression changes. Subsets of genes of interest have been *a priori* defined and changes from baseline of these genes will be assessed. To address the issue of multiple comparisons, metagene analysis, false discovery rate (FDR) or other adjustments will be implemented within each group of genes, as appropriate.~~

~~Sample size requirements for detection of global on-treatment changes in biomarker expression in a multigene platform such as a microarray require many assumptions about structure of the data. Table 13 shows sample size calculations using the approach of Shao and Tseng [Shao, 2007]. This approach assumes 10,000 hypothesis tests with a range of *m* true positive changes, an effect size=1 (δ=1, based on $\log_2$ expression, reflecting a 2-fold change in gene expression), 5% FDR, and detection of 80% of true positives with 80% probability. In addition, a general correlation of 0.1 among all genes is assumed, and a range of possible block-wise correlations in null and alternative genes, as indicated in Table 13 is considered.~~

Table 18 Sample size estimates for a range of data structures

	Number true positives (*m*)		
Correlation	20	200	1000
0.2	48	37	28
0.5	49	38	30
0.8	51	40	31

Based on this assessment, a 1:1 randomization scheme for HER2-enriched cohort and enrolment into treatment arm C for Non-HER2-enriched cohort will be used with approximately 225 subjects to achieve 50 evaluable subjects in each arm. This sample size ensures adequate power for global on-treatment changes in biomarker expression as well as for individual genes, metagenes, or specific subsets of genes of interest. For individual genes or metagenes, the probability of detecting statistically significant gene expression differences between pre-treatment and progression samples, with an effect size of 1 and α=0.05, and a sample size of 50, is >95%. Adjustments for multiple comparisons will be made for groups of individual genes, pre specified in the analysis plan. For example, HER family of receptors and ligands may form a group of genes, with a total of 15 genes in the group (HER Receptors: EGFR, HER2, HER3, HER4; HER Ligands: AR, BTC, EGF, EPGN, EPR, HBEGF, TGFα, NRG1, NRG2, NRG3, and NRG4). In this example, a total of 15 genes would be assessed for on treatment changes in expression, with each comparison having power of >95% (α=0.05, δ=1). In order to adjust for multiple comparisons, FDR at a level of 0.05 would be recommended. Smaller prespecified groups of genes (5 genes or less) may be adjusted using the Bonferroni adjustment.

This sample size will also allow for a sufficient number of subjects to estimate a key secondary endpoint, PFS on next line anti-cancer therapy (PFS-NL). Based on EGF104900, approximately 70% of subjects are expected to continue on next line anti-cancer therapy, thus data from approximately 35 subjects per arm may be available for PFS-NL.

Reason for Change

Section 9.2.2 Sample size sensitivity whole section was removed and changed to "not applicable" due to low enrollment and the early termination of the study

Original Text
Table 14 lists sample size estimations using the data structure, effect size, and FDR rate, as described in Shao and Tseng [Shao, 2007]. If the effect size is larger than expected, the sample size estimates will increase accordingly. On the $\log_2$ scale, an effect size of 1 corresponds to a 2-fold change in gene expression with a standard deviation of 1.0, or a 4-fold change in gene expression with a standard deviation of 2.0, etc. An effect size of 0.8 corresponds to a 2-fold change with a standard deviation of 1.25, or a 3-fold change

with a standard deviation of 2. Similarly, if FDR criteria are relaxed, sample size estimates will decrease. Table 14 examines the impact of a smaller effect size and a larger FDR on sample size estimates, using the correlation structure described in Section 9.2.1

TTable 19 Sample size estimates for a range of data structures

			Number true positives (*m*)		
FDR	Effect Size	Correlation	20	200	1000
0.05	1.0	0.2	48	37	28
0.05	1.0	0.5	49	38	30
0.05	1.0	0.8	**51**	40	31
0.10	1.0	0.2	46	34	25
0.10	1.0	0.5	49	36	27
0.10	1.0	0.8	51	39	30
0.05	0.8	0.2	78	58	44
0.05	0.8	0.5	83	63	49
0.05	0.8	0.8	88	68	53
0.10	0.8	0.2	72	52	38
0.10	0.8	0.5	77	57	42
0.10	0.8	0.8	81	61	46

For individual genes or metagenes, the probability of detecting a statistically significant on treatment difference, with an effect size of 0.8 and α=0.05, and a sample size of 50, is >95%.

Amended Text
Not applicable

~~Table 14 lists sample size estimations using the data structure, effect size, and FDR rate, as described in Shao and Tseng [Shao, 2007]. If the effect size is larger than expected, the sample size estimates will increase accordingly. On the $\log_2$ scale, an effect size of 1 corresponds to a 2-fold change in gene expression with a standard deviation of 1.0, or a 4-fold change in gene expression with a standard deviation of 2.0, etc. An effect size of 0.8 corresponds to a 2-fold change with a standard deviation of 1.25, or a 3-fold change with a standard deviation of 2. Similarly, if FDR criteria are relaxed, sample size estimates will decrease. Table 14 examines the impact of a smaller effect size and a larger FDR on sample size estimates, using the correlation structure described in Section 9.2.1~~

Table 20 Sample size estimates for a range of data structures

			Number true positives (*m*)		
FDR	Effect Size	Correlation	20	200	1000
0.05	1.0	0.2	48	37	28
0.05	1.0	0.5	49	38	30
0.05	1.0	0.8	**51**	40	31
0.10	1.0	0.2	46	34	25
0.10	1.0	0.5	49	36	27
0.10	1.0	0.8	51	39	30
0.05	0.8	0.2	78	58	44
0.05	0.8	0.5	83	63	49
0.05	0.8	0.8	88	68	53
0.10	0.8	0.2	72	52	38
0.10	0.8	0.5	77	57	42
0.10	0.8	0.8	81	61	46

For individual genes or metagenes, the probability of detecting a statistically significant on treatment difference, with an effect size of 0.8 and α=0.05, and a sample size of 50, is >95%.

Reason for Change

Section 9.3.3.1 The primary objective is updated to describe the change in biomarkers related to the specified mechanisms in the pre-treatment biopsy and the progression biopsy with each arm**.** The data cut-off for the primary analysis will be defined at 12 months after the last subject was enrolled in the study or after the last subject progressed/withdrew, whichever is earlier. End of Study was re-defined.

Original Text

The primary objective will be achieved through a test of the hypothesis (see Section 9.1) evaluating the change in biomarkers related to the specified mechanisms in the pre-treatment biopsy and the progression biopsy with each arm.

- The primary analysis of changes in biomarker expressions and evaluation of PFS and PFS-NL will be performed approximately 12 months after the last subject is randomized. This will allow for exploring the association between on-treatment

changes in biomarkers and PFS-NL. Other secondary endpoints will also be reported to compliment the primary analysis. The second and final analysis for OS will be performed at the time when

- 75% of the subjects have died
- 100% of subjects have completed study treatment;
- all subjects who go onto first next line therapy have completed first next line therapy.

Details on the handling of missing data are provided in Section 9.3.5

Amended Text

The primary objective will be achieved by describing the change in biomarkers related to the specified mechanisms in the pre-treatment biopsy and the progression biopsy with each arm.

~~The primary objective will be achieved through a test of the hypothesis (see Section 9.1) evaluating the change in biomarkers related to the specified mechanisms in the pre-treatment biopsy and the progression biopsy with each arm.~~

The data cut-off for the primary analysis will be defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier. Following the cut-off date for the primary analysis, the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:

- **All patients have died or discontinued from the study**
- **Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study**
- **At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.** ~~The primary analysis of changes in biomarker expressions and evaluation of PFS and PFS-NL will be performed approximately 12 months after the last subject is randomized. This will allow for exploring the association between on-treatment changes in biomarkers and PFS-NL. Other secondary endpoints will also be reported to compliment the primary analysis. The second and final analysis for OS will be performed at the time when~~

~~• 75% of the subjects have died~~

~~• 100% of subjects have completed study treatment;~~

~~• all subjects who go onto first next line therapy have completed first next line therapy. Section 9.3.5.~~

Reason for Change

Section 9.3.5 No adjustments for multiple comparisons will be made as there is no formal hypothesis testing. Removed the sentence for the analysis of OS regarding the last date of known contact

Original Text

For the analysis of OS, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored.

For the analysis of PFS, if the subject received subsequent anticancer therapy prior to the date of documented progression or death, PFS will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

Details on the determination of tumor response are given in Section 7.3.4.

For the primary objective, adjustments for multiple comparisons will be as described in Section 9.2.1.

Amended Text

~~For the analysis of OS, the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored.~~

For the analysis of PFS **during study treatment period**, if the subject received subsequent anticancer therapy prior to the date of documented progression or death, PFS will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP.

Details on the determination of tumor response are given in Section 7.3.4.

No adjustments for multiple comparisons will be made as there is no formal hypothesis testing.

~~For the primary objective, adjustments for multiple comparisons will be as described in Section 9.2.1.~~

Reason for Change

Section 9.3.5.1.1 The primary biomarker endpoint was updated to be the change in expression/percent presence levels of biomarkers as measured in tissue from the progression tumor biopsy, compared with expression/percent presence levels of these markers as measured in the screening tumor biopsy. Marker levels may be derived from measurements of mRNA or protein from biopsy samples or changes in blood-derived biomarkers.

Original Text

The primary biomarker endpoint is change in expression levels of biomarkers as measured in tissue from the progression tumor biopsy, compared with expression levels of these markers as measured in the screening tumor biopsy. Marker levels may be derived from measurements of mRNA or protein from biopsy samples or changes in blood-derived biomarkers.

The primary endpoint of changes in biomarker expression will be analyzed using paired t-tests or related nonparametric approaches, or paired analysis of metagenes, as appropriate. This will be done within each treatment arm. This analysis will be done using the Evaluable Population, which will consist of all subjects who were assigned to study treatment and have both baseline and progression biopsies available. Further details will be described in the RAP.

Amended Text

The primary biomarker endpoint is change in expression/percent presence levels of biomarkers as measured in tissue from the progression tumor biopsy, compared with expression/percent presence levels of these markers as measured in the screening tumor biopsy. Marker levels may be derived from measurements of mRNA or protein from biopsy samples.

~~The primary biomarker endpoint is change in expression levels of biomarkers as measured in tissue from the progression tumor biopsy, compared with expression levels of these markers as measured in the screening tumor biopsy. Marker levels may be derived from measurements of mRNA or protein from biopsy samples or changes in blood-derived biomarkers.~~

The primary endpoint of changes in biomarker expression will be presented for each treatment arm for the evaluable population. Due to limited number of subjects enrolled as well as limited number of subjects with baseline biopsy and biopsy at disease progression, no statistical analyses will be performed.

~~The primary endpoint of changes in biomarker expression will be analyzed using paired t-tests or related nonparametric approaches, or paired analysis of metagenes, as appropriate. This will be done within each treatment arm. This analysis will be done using the Evaluable Population, which will consist of all subjects who were assigned to study treatment and have both baseline and progression biopsies available. Further details will be described in the RAP.~~

Reason for Change

Section 9.3.5.1.2 Overall Survival, Progression Free Survival on new anticancer treatment, association between progression changes in biomarkers and PFS on next line of anticancer treatment were removed

Original Text

Overall survival is defined as the time from randomization until death due to any cause. For subjects who do not die, time of death will be censored at the date of last contact. This analysis will be done using the ITT population.

Overall survival will be summarized using Kaplan-Meier curves. The Pike estimator [Berry, 1991] of the treatment HR based on the log-rank test along with 95% CIs will be provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median OS time and the first and third quartiles will be presented along with approximate 95% CIs.

These analyses will be done on the ITT population.

Amended Text

~~**Overall Survival**~~

~~Overall survival is defined as the time from randomization until death due to any cause. For subjects who do not die, time of death will be censored at the date of last contact. This analysis will be done using the ITT population.~~

~~Overall survival will be summarized using Kaplan-Meier curves. The Pike estimator [Berry, 1991] of the treatment HR based on the log-rank test along with 95% CIs will be provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median OS time and the first and third quartiles will be presented along with approximate 95% CIs.~~

~~These analyses will be done on the ITT population.~~

Reason for Change

Section 9.3.5.5 PRO and HRQOL were removed

Original Text
The objective of collecting PRO and HRQOL data is to describe the PRO and HRQOL of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy. It has been found in some studies that chemotherapies have significant detrimental impact on cancer patients. For example, in Hwang et al (2013) [Hwang,2013] study on adjuvant breast cancer patients, they found that breast cancer patients who underwent adjuvant chemotherapy experienced significantly worse quality of life than those who did not receive chemotherapy. It is valuable to understand whether chemotherapy has impact on PRO and HRQOL in the metastatic setting, and also what

adverse events associated with chemotherapy contribute to the changes of PRO and HRQOL. PRO and HRQOL data will be collected using FACT-B and Multidimensional Assessment of Fatigue (MAF) scales. These data will be collected at baseline, week 3, week 6, week 12, and discontinuation/end of the study. Further details on PRO and HRQOL analyses will be addressed in the RAP.

Amended Text

~~The objective of collecting PRO and HRQOL data is to describe the PRO and HRQOL of trastuzumab in combination with lapatinib and of trastuzumab in combination with chemotherapy. It has been found in some studies that chemotherapies have significant detrimental impact on cancer patients. For example, in Hwang et al (2013) [Hwang,2013] study on adjuvant breast cancer patients, they found that breast cancer patients who underwent adjuvant chemotherapy experienced significantly worse quality of life than those who did not receive chemotherapy. It is valuable to understand whether chemotherapy has impact on PRO and HRQOL in the metastatic setting, and also what adverse events associated with chemotherapy contribute to the changes of PRO and HRQOL. PRO and HRQOL data will be collected using FACT-B and Multidimensional Assessment of Fatigue (MAF) scales. These data will be collected at baseline, week 3, week 6, week 12, and discontinuation/end of the study. Further details on PRO and HRQOL analyses will be addressed in the RAP.~~

Reason for Change

Section 10.5 End of study assessment and follow up were re-fined for the purpose of site closure per section 7.

Original Text

The study will end when all criteria below are met:

- 75% of the subjects have died
- 100% of subjects have completed study treatment;
- all subjects who go onto first next line therapy have completed first next line therapy.

Amended Text

The study will end **when all subjects have completed the study, i.e. presented with disease progression, started new anti-cancer therapy, died or withdrew from the study (whichever came first) during the study treatment period or the follow-up period after discontinuation due to any reasons in the absence of other than disease progression.** ~~when all criteria below are met:~~

All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal of consent or any other reasons mentioned in section 4.2.1.
In case of disease progression during the treatment period, the subject will be followed-up for 30 days for safety evaluation and no further study-specific follow-up will be carried out; the subject will be considered as having completed the study. Similarly, in case of disease progression after the treatment period (i.e. in subjects who discontinued for any reasons other than disease progression) and before the end of the study, no further study-specific follow-up will be carried out; the subject will be considered as having completed the study.

In case of study treatment discontinuation for any reasons other than disease progression, the subjects will be followed-up for safety and efficacy assessments (disease assessments done every 9 weeks until Week 54, then every 24 weeks) until disease progression, new anticancer therapy, death, withdrawal of consent or end of study, whichever comes first.

~~75% of the subjects have died~~ **Following the cut-off date for the primary analysis (defined at 12 months after the last subject enrolled in the study or the last subject progressed/withdrew, whichever is earlier), the study will remain open. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, as long as subjects derive benefit from lapatinib. The end of study defined as the earliest occurrence of one of the following:**

- **All patients have died or discontinued from the study**
- **Another clinical study becomes available that can continue to provide lapatinib in this patient population and all subjects ongoing are eligible to be transferred to that clinical study**
- **At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.**

~~100% of subjects have completed study treatment;~~

~~All subjects who go onto first next line therapy have completed first next line therapy.~~

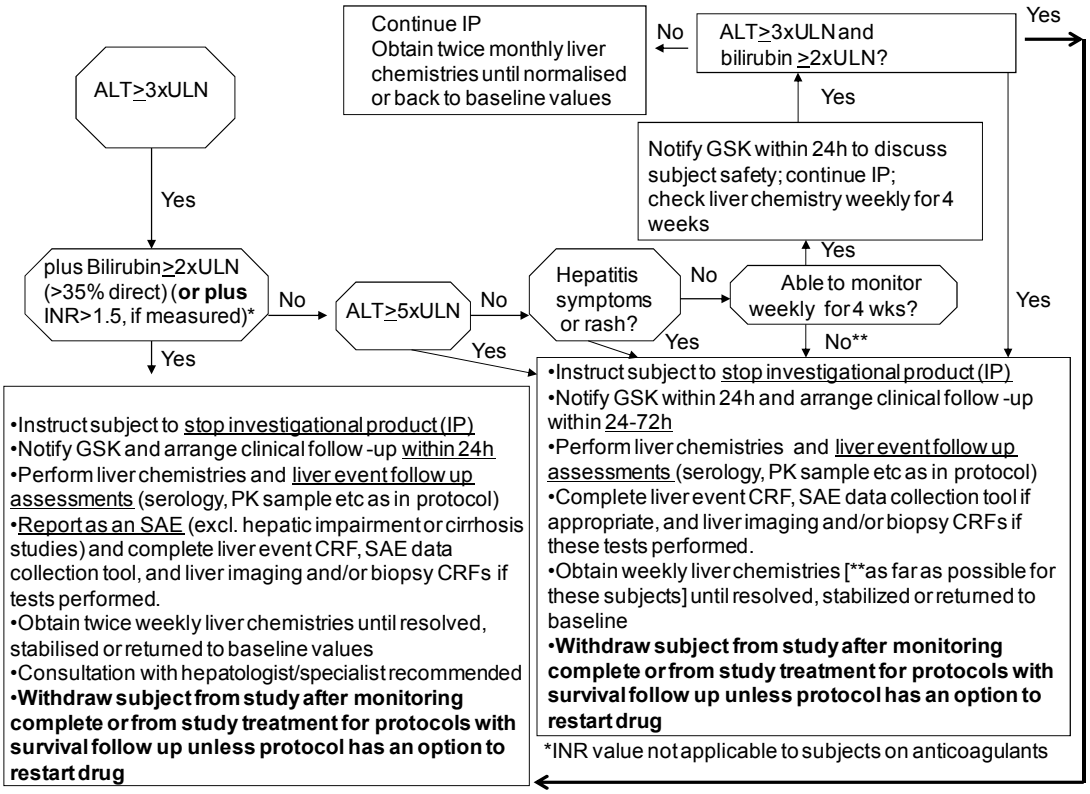
Reason for Change

[redacted]

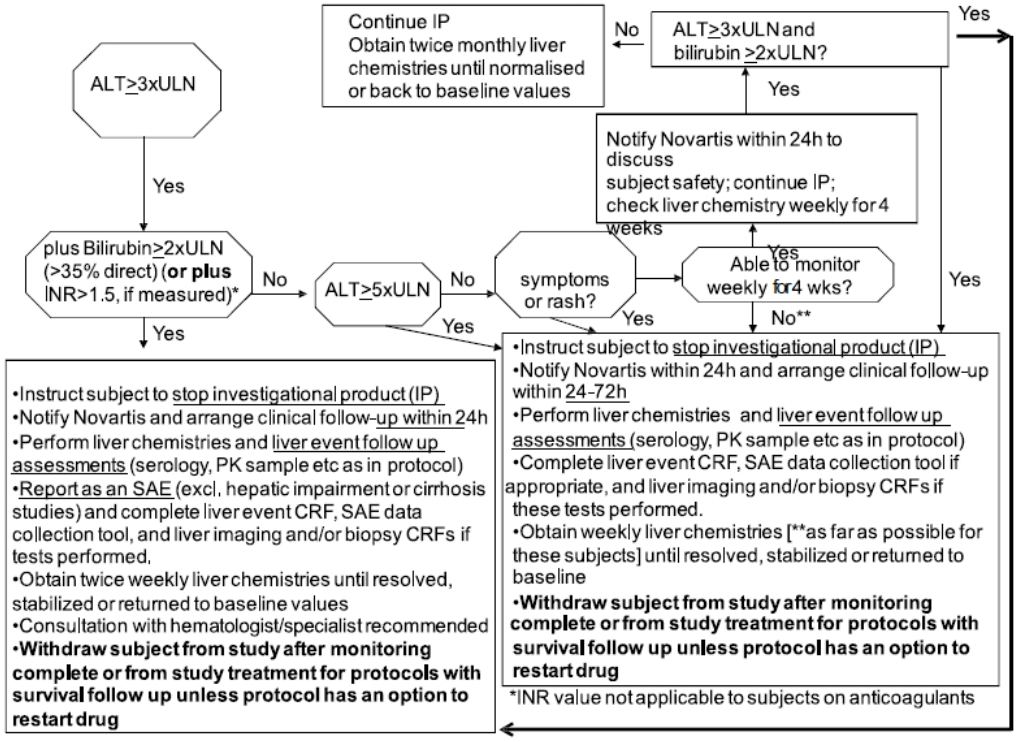
Reason for Change

Section 12.4. Appendix 4: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria was updated to remove GSK

Original Text



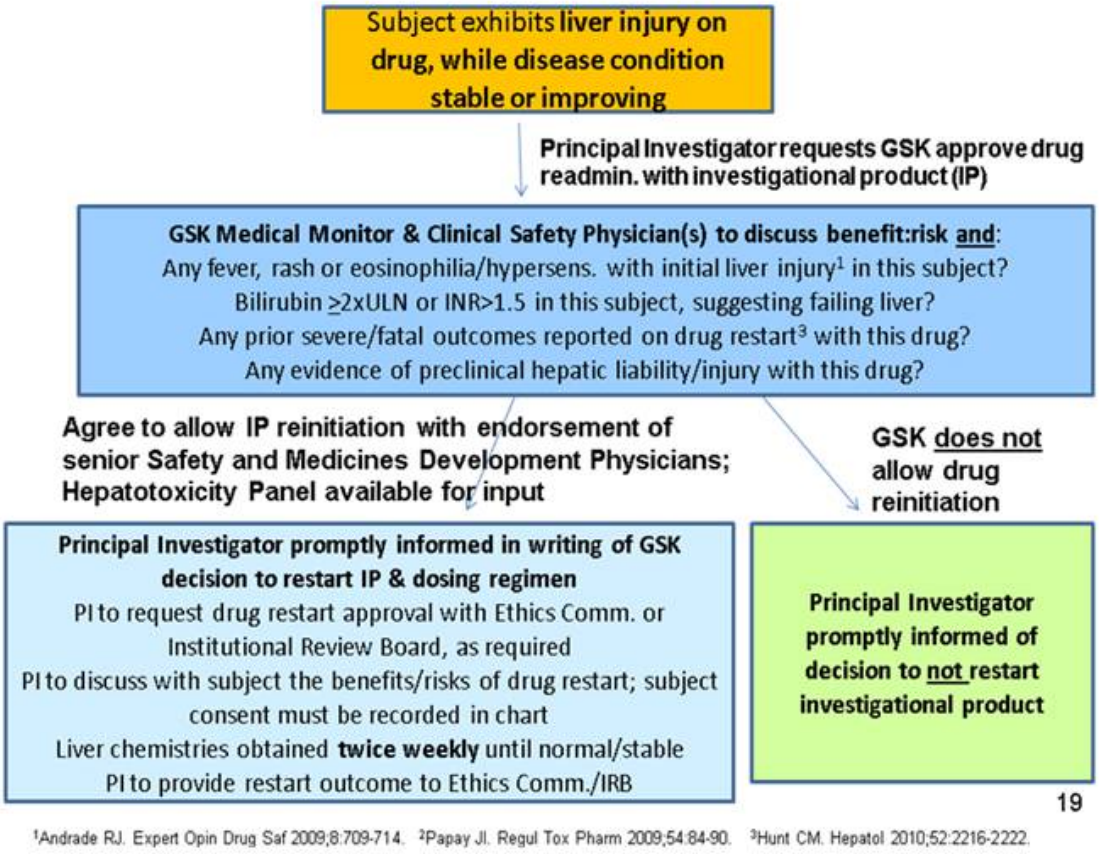
Amended Text



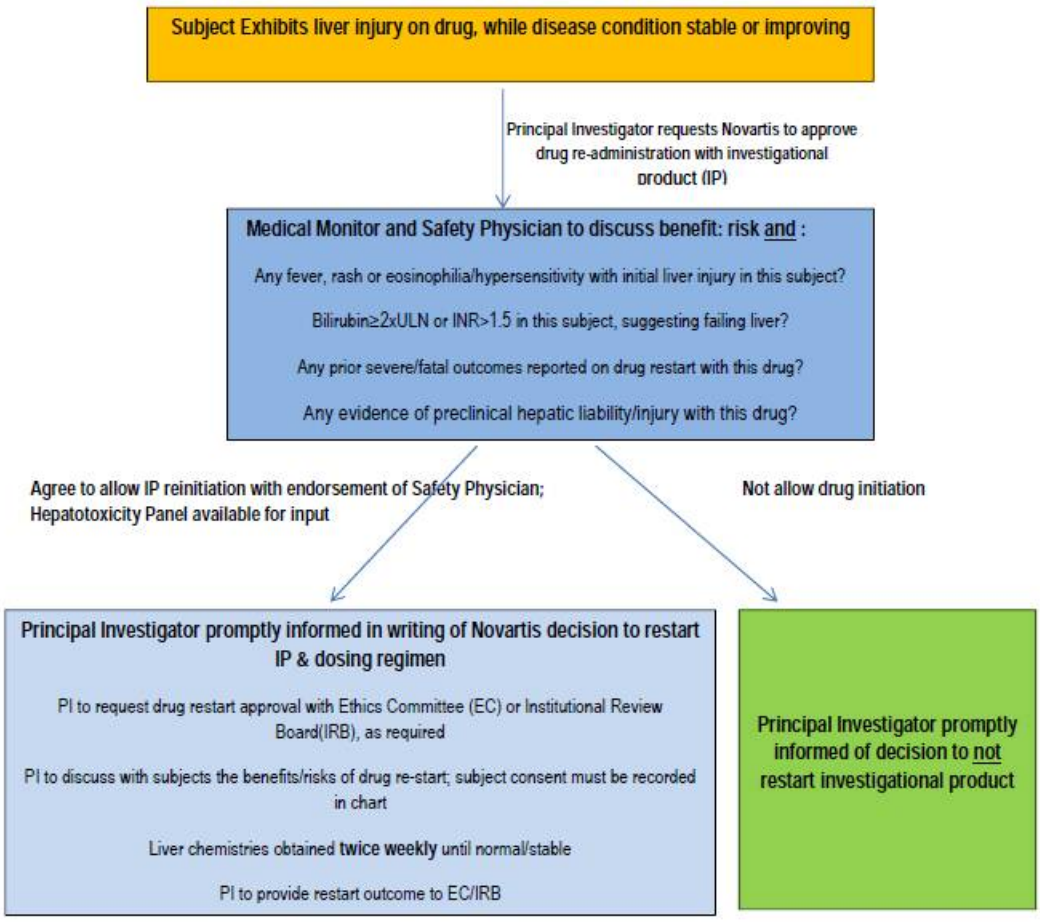
Reason for Change

Section 12.5 Appendix 5 Figure 2 and Figure 3 were updated to remove GSK

Original Text



Amended Text



Andrade RJ. Expert Opin Drug Saf 2009; 8:709-714. Papay JL. Regul Tox Pharm 2009; 54:84-90. Hunt, CM. Heptol. 2010; 52: 2216-2222

Reason for Change

List of references was updated to reflect changes in the references in the protocol.

Added References

Bianchini G, Pienkowski T, Im YH, et al (2016) Residual disease after HER2-directed therapies in the neosphere study: Modulation of tumor lymphocyte infiltration (TIL) and prognosis. J Clin Oncol 34 (suppl; abstr 517).

Denkert C, Loibl S, Noske A, et al (2010) Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol.;28(1):105-13.

Denkert C, von Minckwitz G, Brase JC, et al (2015) Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol.;33(9):983-91.

Dieci MV, Bisagni G, Cagossi K, et al (2015) Tumor infiltrating lymphocytes and correlation with outcome in the Cher-LOB study. Cancer Res (9 Supplement) SABCS14-PD1-1, 1538-7445.

Hannesdóttir L, Tymoszuk P, Parajuli N, et al (2013) Lapatinib and doxorubicin enhance the Stat1-dependent antitumor immune response. Eur J Immunol.;43(10):2718-29. Ignatiadis M, et al. J Clin Oncol. 2012 Jun 1;30(16):1996-2004

Issa-Nummer Y, Darb-Esfahani S, Loibl S, et al (2013) Prospective validation of immunological infiltrate for prediction of response to neoadjuvant chemotherapy in HER2-negative breast cancer--a substudy of the neoadjuvant GeparQuinto trial. PLoS One.;8(12):e79775. Laoui D, et al. Eur. J. Immunol. 2013. 43: 2538–2542

Loi S, Sirtaine N, Piette F, et al. (2013) Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol.;31(7):860-7.

Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, Kellokumpu-Lehtinen PL, Bono P, Kataja V, Desmedt C, Piccart MJ, Loibl S, Denkert C, Smyth MJ, Joensuu H, Sotiriou C (2014) Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544-50.

Sobottka B, Pestalozzi B, Fink D, et al (2016) Similar lymphocytic infiltration pattern in primary breast cancer and their corresponding distant metastases. Oncoimmunology. 5;5(6):e1153208.

Urruticoechea A, Rizwanullah M, Im SA, et al (2016) PHEREXA: A phase III study of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. J Clin Oncol 34, 2016 (suppl; abstr 504)

Updated References

Lapatinib Summary of Product Characteristics. ~~Glaxo Group Ltd, UK. 06 May 2013~~. **Novartis Europharm Limited, UK. 11 August 2015**.

~~TYKERB~~ **TYVERB** (lapatinib) ~~Product Information. June, 2013.~~ **Package Leaflet. Novartis Europharm Limited, UK. 11 August 2015**.

Deleted References

~~Hanker LC, Rody A, Holtrich U, Pusztai L, et al. Prognostic evaluation of the B cell/IL-8 metagene in different intrinsic breast cancer subtypes. *Breast Cancer Res Treat*. 2013; 137(2): 407-16.Huehn J, Plansky J, Hamann A. Epigenetic control of FOXP3 expression: the key to a stable regulatory T-cell lineage. Nat Rev Immunol. 2009; 9: 83-9.~~

Kroemer G, Galluzzi L, Kepp O, Zitvogel L, et al. Immunogenic cell death in cancer therapy. *Annu Rev Immunol*. 2013; 31: 51-72.

Melero I, Grimaldi AM, Perez-Gracia JL, Ascierto PA. Clinical development of immunostimulatory monoclonal antibodies and opportunities for combination. *Clin Cancer Res*. 2013; 19(5): 997-1008.

Nagalla S, Chou J, Willingham M, et al. Interactions between immunity, proliferation and molecular subtype in breast cancer prognosis. *Genome Biol*. 2013; 14(4): R34.

O'Connor R. A review of mechanisms of circumvention and modulation of chemotherapeutic drug resistance. *Curr Cancer Drug Targets*. 2009; 9(3): 273-80.

Rody A, Holtrich U, Pusztai L, Liedtke C. T-cell metagene predicts a favorable prognosis in estrogen receptor-negative and HER2-positive breast cancers. *Breast Cancer Res*. 2009; 11(2): R15.

Shao Y, Tseng C-H. Sample size calculation with dependence adjustment for FDR-control in microarray studies. *Stat Med*. 2007; 26: 4219-37.

Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol*. 2011; 29: 235-71.

12.10.3. Protocol Amendment 3

Due to the sponsorship transfer from GSK to Novartis, references to GSK and GSK roles have been replaced with Novartis and Novartis roles. Additionally, administrative changes have been made to align with Novartis processes and procedures.

Reason for Change:

Front page and the following page have been updated to comply with the Novartis protocol template

Original Text:

TITLE PAGE

Division: Worldwide Development
Information Type: Clinical Protocol

Title:	An Open-Label, Phase II, Study to Evaluate Biomarkers Associated with Response to Subsequent Therapies in Subjects with HER2-Positive Metastatic Breast Cancer Receiving Treatment with Trastuzumab in Combination with Lapatinib or Chemotherapy (EGF117165)

Compound Number: GW572016

Development Phase II

Effective Date: 23-MAR-2017 (final)

Amended Text:

Clinical Development

GW572016

Protocol EGF114299

An Open-Label, Phase II, Study to Evaluate Biomarkers Associated with Response to Subsequent Therapies in Subjects with HER2-Positive Metastatic Breast Cancer Receiving Treatment with Trastuzumab in Combination with Lapatinib or Chemotherapy

Authors [redacted]

Document type	**Amended Protocol Version (Clean)**
EUDRACT number	**2014-001220-30**
Version number	**03**
Development phase	**Phase II**
Document status	**Final**
Release date	**15-May-2017**
Novartis internal reference number	**CLAP016A2206**

Amendment 3

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GW572016, the purpose of this protocol Amendment 3 is to:

- **Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;**
- **Make administrative changes to align with Novartis processes and procedures;**

As of May 2017:

42 patients have received study treatment in five countries;

34 patients have completed or discontinued study treatment.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

~~TITLE PAGE~~

~~**Division:** Worldwide Development~~
~~**Information Type:** Clinical Protocol~~

~~**Title:**~~	~~An Open-Label, Phase II, Study to Evaluate Biomarkers Associated with Response to Subsequent Therapies in Subjects with HER2-Positive Metastatic Breast Cancer Receiving Treatment with Trastuzumab in Combination with Lapatinib or Chemotherapy (EGF117165)~~

~~**Compound Number:** GW572016~~

~~**Development Phase** II~~

~~**Effective Date:** 23-MAR-2017 (final)~~

Reason for Change:

Enrolment was halted and the text in the description section has been updated to past tense. Authors are included on front page and have therefore been deleted in this section.

Original Text:

Description: This is a multicenter, open-label, Phase II study in subjects with HER2-positive metastatic breast cancer who received at least 2 prior lines of anti-HER2-targeted therapies of which at least one included a trastuzumab-containing regimen. Eligible subjects will have confirmed HER2-positive and hormonal status from a biopsy taken at screening (pre-treatment biopsy). Subjects will have consented to a subsequent biopsy at disease progression. Subjects will be assigned to one of two cohorts based on the molecular subtype of the pre-treatment biopsy by Prosigna. Eligible subjects with a HER2-enriched molecular subtype will be randomized in a 1:1 ratio to 1 of 2 treatment arms: trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily) or trastuzumab in combination with chemotherapy of the investigator's choice (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg q3weekly infusions and chemotherapy as decided by investigator). Eligible subjects with breast cancer classified as a molecular subtype complementary to the HER2-enriched referred to as Non-HER2-enriched (i.e., luminal A, luminal B or basal-like) will be enrolled into an additional arm treated with trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily). Subjects with hormone receptor positive breast cancer assigned to receive treatment with lapatinib and trastuzumab will be required to receive concomitant endocrine therapy with an aromatase inhibitor of the investigator's choice. Subjects with hormone receptor-positive disease assigned to the treatment arm of trastuzumab in combination with chemotherapy may receive concomitant endocrine therapy with an aromatase inhibitor, of the investigator's choice and at the discretion of the investigator. All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal or any other reasons mentioned in section 4.2.1. The primary endpoint is to evaluate the changes in the expression of biomarkers associated with immunomodulation between the progression biopsy and the pre-treatment biopsy within each arm. Secondary efficacy endpoints include overall response rate; clinical benefit rate; and progression-free survival (PFS) on treatment; as well as safety/tolerability. Due to difficulty in enrolling subjects, enrollment will be

halted and the study will be terminated early. No formal comparisons between treatment arms will be undertaken.

Subject: lapatinib, HER2-overexpressing metastatic breast cancer, trastuzumab, ErbB2, HER2, biomarker, PAM50, HER2-enriched, Prosigna

Author(s): [redacted]

Amended text:

Description: This is a multicenter, open-label, Phase II study in subjects with HER2-positive metastatic breast cancer who received at least 2 prior lines of anti-HER2-targeted therapies of which at least one included a trastuzumab-containing regimen. Eligible subjects will have confirmed HER2-positive and hormonal status from a biopsy taken at screening (pre-treatment biopsy). Subjects will have consented to a subsequent biopsy at disease progression. Subjects will be assigned to one of two cohorts based on the molecular subtype of the pre-treatment biopsy by Prosigna. Eligible subjects with a HER2-enriched molecular subtype will be randomized in a 1:1 ratio to 1 of 2 treatment arms: trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily) or trastuzumab in combination with chemotherapy of the investigator's choice (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg q3weekly infusions and chemotherapy as decided by investigator). Eligible subjects with breast cancer classified as a molecular subtype complementary to the HER2-enriched referred to as Non-HER2-enriched (i.e., luminal A, luminal B or basal-like) will be enrolled into an additional arm treated with trastuzumab in combination with lapatinib (trastuzumab loading dose of 8 mg/kg followed by 6-mg/kg infusions every 3 weeks (q3weekly) and 1000 mg of lapatinib once daily). Subjects with hormone receptor positive breast cancer assigned to receive treatment with lapatinib and trastuzumab will be required to receive concomitant endocrine therapy with an aromatase inhibitor of the investigator's choice. Subjects with hormone receptor-positive disease assigned to the treatment arm of trastuzumab in combination with chemotherapy may receive concomitant endocrine therapy with an aromatase inhibitor, of the investigator's choice and at the discretion of the investigator. All subjects will receive study treatment until disease progression, death, unacceptable toxicity, subject withdrawal or any other reasons mentioned in section 4.2.1. The primary endpoint is to evaluate the changes in the expression of biomarkers associated with immunomodulation between the progression biopsy and the pre-treatment biopsy within each arm. Secondary efficacy endpoints include overall response rate; clinical benefit rate; and progression-free survival (PFS) on treatment; as well as safety/tolerability. Due to difficulty in enrolling subjects, enrolment **was** ~~will be~~ halted and the study will be terminated early. No formal comparisons between treatment arms will be undertaken.

Subject: lapatinib, HER2-overexpressing metastatic breast cancer, trastuzumab, ErbB2, HER2, biomarker, PAM50, HER2-enriched, Prosigna

~~Author(s):~~ [redacted]

Reason for Change:

Description of protocol amendment number 3 has been added to Revision Chronology section

Original Text:

N/A

Amended Text:

2013N170247_03	**15-May-2017**	**Amendment No. 03: Global amendment:** **Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents.** **Make administrative changes to align with Novartis processes and procedures.**

Reason for Change:

Sponsor signature page has been updated to comply with the Novartis protocol template.

Original Text:

[redacted]Signature:

Date

Dr. [redacted]
Novartis Pharma AG
Postfach
4002 Basel
Switzerland
Telephone: [redacted]

Amended Text:

Sponsor Signatory: **Signature** **Date**

Dr. [redacted] _____ _____

[redacted] ~~Signature:~~

_____ _____

~~**Date**~~

~~*Dr.*~~ [redacted]

~~*Postfach*~~
~~*4002 Basel*~~
~~*Switzerland*~~
~~*Telephone:*~~ [redacted]

Reason for Change:

Sponsor contact information has been updated to Novartis contact information and the IND number for the study has been added.

Original Text:

SPONSOR INFORMATION PAGE

Clinical Study Identifier: EGF117165

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: [redacted]

GlaxoSmithKline Research & Development Limited
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: [redacted]

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Medical Monitor Contact Information

Dr. [redacted]
[redacted]
Novartis Pharma AG
Postfach
4002 Basel
Switzerland
Telephone: [redacted]

Regulatory Agency Identifying Number(s):

Eudra CT number: 2014-001220-30

Amended Text:

SPONSOR INFORMATION PAGE

Clinical Study Identifier: EGF117165

~~Sponsor Legal Registered Address~~

~~GlaxoSmithKline Research & Development Limited~~
~~980 Great West Road~~
~~Brentford~~
~~Middlesex, TW8 9GS~~
~~UK~~

Sponsor Contact ~~Address~~ **Information**

Novartis Pharma Services AG

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Serious Adverse Events (SAE) Contact Information:

Please refer to the study procedures manual.

For study conduct questions not related to patient safety, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available, please contact the Medical Lead.

[redacted] Contact Information**:**

~~Dr.~~ [redacted] **MD, PhD**
[redacted]
Novartis Pharma AG
Postfach **CH-4002 Basel**
~~CH-4002 Basel~~
Switzerland
Telephone: [redacted]
Email: [redacted]

~~GlaxoSmithKline Research & Development Limited~~
~~Iron Bridge Road~~
~~Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK~~
~~Telephone: [redacted]~~

~~GlaxoSmithKline Research & Development Limited~~
~~1250 South Collegeville Road~~
~~Collegeville, PA 19426, USA~~
~~Telephone Number:~~ [redacted]

~~In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.~~

Regulatory Agency Identifying Number(s):

Eudra CT number: 2014-001220-30

IND Number: 61362

Reason for Change:

To align with Novartis processes and procedures.

Original Text:

Section 7.4.3 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or study treatment must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported within 24 hours, as indicated in Section 7.4.5.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up.

Amended Text:

Section 7.4.3 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time **a subject consents to participate in the study** ~~the first dose of study treatment is administered~~ until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs **(irrespective of causality)** will be collected over the same time period as stated above for AEs. In addition, any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or study treatment must be recorded **promptly to Novartis** from the time a subject consents to participate in the study up to and including any follow-up contact, as indicated in section 7.4.5 **and Table 12**.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up.

Reason for Change:

To align with Novartis processes and procedures. Additional, with the update to section 7.4.3, there is a referral to the table with events and reporting timelines and table number and table title have therefore been added.

Original Text:

Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
CV events or death	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and bilirubin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

1. Liver chemistry elevations should be notified at onset to discuss subject safety.

2. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible
3. .INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Amended Text:

Table 12 Time and Events

Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
CV events or death	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	~~2 Weeks~~ **24 hours**	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and bilirubin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

4. Liver chemistry elevations should be notified at onset to discuss subject safety.

5. Liver Event Documents (i.e., “Liver Event CRF” and “Liver Imaging CRF” and/or “Liver Biopsy CRF”, as applicable) should be completed as soon as possible
6. .INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Reason for Change:

Dublicate text removed.

Original Text:

7.4.6 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met.

There is a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Notification will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Amended Text:

7.4.6 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met.

There is a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Notification will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority~~, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)~~ and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Reason for Change:

To align with Novartis processes and procedures.

Original Text:

7.4.7.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

Amended Text:

7.4.7.2 Pregnancy Reporting

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to ~~GSK~~ **Novartis** within ~~2 weeks~~ **24 hours** of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to ~~GSK~~ **Novartis**.

Reason for Change:

Enrolment was halted and the text has been updated to past tense. The status of enrolment per 31 Jul 2016 was deleted as it is no longer relevant.

Original Text:

9.2.1 Sample Size Assumptions

This is a purely descriptive study. Due to difficulty in enrolling subjects into this trial, future enrolment will be halted and the study will be terminated early. Up to 31 Jul 2016, 29 patients have been enrolled.

A pre-treatment biopsy and a biopsy at disease progression will provide the samples for biomarker analysis.

Amended text:

9.2.1 Sample Size Assumptions

This is a purely descriptive study. Due to difficulty in enrolling subjects into this trial, future enrolment **was** ~~will be~~ halted and the study will be terminated early. ~~Up to 31 Jul 2016, 29 patients have been enrolled.~~

This is a purely descriptive study. Due to difficulty in enrolling subjects into this trial, future enrolment was halted and the study will be terminated early.

Reason for Change:

To align with Novartis processes and procedures.

Original Text:

10.6 Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time

will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

Amended Text:

10.6 Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a ~~GSK~~ **Novartis** audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

~~GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.~~ **Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines**.

The investigator must notify ~~GSK~~ **Novartis** of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

Reason for Change:

To align with Novartis processes and procedures.

Original Text:

10.7 Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript may be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Amended Text:

10.7 Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ~~GSK~~ **Novartis** site or other mutually-agreeable location.

~~GSK~~ **Novartis** will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The sponsor aims to post a results summary to the Novartis Clinical Study Trial results website (www.novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of the study report, Novartis

aims to submit results of the study for publication. When publication is not feasible, please refer to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results. A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

~~The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript may be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.~~

~~When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.~~