PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB+HERCEPTIN+DOCETAXEL VERSUS PLACEBO+HERCEPTIN+DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	YO29296
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
NCT NUMBER	*NCT02896855*
TEST PRODUCT:	Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann–La Roche Ltd
DATE FINAL:	Version 1: 19 November 2013
DATE AMENDED:	Version 2: 19 April 2016 Version 3: 10 May 2017 Version 4: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
07-Mar-2020 16:18:59	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol YO29296 has been amended primarily to incorporate a crossover option for patients in Arm A (placebo + Herceptin + docetaxel) who are still receiving study treatment to receive pertuzumab in place of placebo. Changes to the protocol, along with a rationale for each change, are summarized below:

- At the primary analysis (2018), clinically meaningful improvement in the primary efficacy endpoint of investigator-assessed PFS was demonstrated. As a result, and given a high unmet need in patients with HER2 metastatic breast cancer in China, patients in Arm A who are still receiving study treatment will be offered the option to cross over and receive pertuzumab (in place of placebo) in addition to Herceptin and docetaxel, upon approval of protocol YO29296 Version 4 (Sections 3.1, 4.2, 4.3.1.1, and 4.3.2.1).
- All patients who are still receiving study treatment at the time of the end of the study will continue to be offered study treatment until disease progression or unacceptable toxicity (Sections 3.1 and 4.3.4).
- Patients may be eligible to receive pertuzumab as part of an extension study (Study MO29406), if eligible (Sections 3.1, 3.1.1, and 4.3.4).
- The definition of end of study has been updated to reflect patient cross-over from Arm A to the pertuzumab arm and continuation of treatment as outlined above (Section 3.2).

Other changes made to the protocol are as follows:

- Language has been added to the safety objective to clarify that patients in Arm A who cross over or continue to receive study treatment without placebo will be included as an independent population in safety analyses (Section 2.2).
- The frequency of tumor assessments and prospective collection of tumor scans has been modified to align with local clinical practice (Sections 3.1 and 4.5.6; Appendix 1).
- The obligation for confirmation of complete and partial responses has been removed from tumor and response evaluations, as these confirmations are not required per RECIST v1.1 (Section 4.5.6).
- Language regarding the adverse event reporting period and reporting of adverse events that occur after the adverse event reporting period has been updated to align with current guidelines (Sections 5.3.1, 5.4.2.2, and 5.6).
- Emergency Medical Contact information has been updated with new primary and secondary contacts (Section 5.4.1). The Medical Monitor has also been updated where applicable in the protocol.
- The study visit window has been modified to accommodate the possibility of holidays, vacations, and unforeseen major life events (Appendix 1).

- The time window for acceptable results from standard-of-care tests or examinations performed prior to the initiation of study treatment has been clarified (Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB+HERCEPTIN+DOCETAXEL VERSUS PLACEBO+HERCEPTIN+DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	YO29296
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
NCT NUMBER	*NCT02896855*
TEST PRODUCT:	Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann–La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB + HERCEPTIN + DOCETAXEL VERSUS PLACEBO + HERCEPTIN + DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	YO29296
VERSION NUMBER:	4
TEST PRODUCT:	Pertuzumab (RO4368451)
PHASE:	III
INDICATION:	HER2-positive metastatic breast cancer that has not been treated with chemo or biologic therapy
SPONSOR:	F. Hoffmann–La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of pertuzumab plus Herceptin plus docetaxel compared with placebo plus Herceptin plus docetaxel in patients with previously untreated HER2-positive metastatic breast cancer (MBC), as measured by investigator-assessed progression-free survival (PFS)

The secondary efficacy objectives for this study are as follows:

- To compare overall survival (OS) between the two treatment arms
- To compare the objective response rate between the two treatment arms
- To compare the duration of objective response between the two treatment arms

Exploratory Objective

The exploratory objective for this study is as follows:

- To explore the relationship of biomarkers, such as PI3K status, HER2/3 mRNA, PD-L1, and CD8 expression, with efficacy (response rate, PFS, and OS)

Safety Objective

The safety objective for this study is as follows:

- To compare the safety profile between the two treatment arms *(including crossover patients and those no longer receiving placebo)*

Study Design

Description of Study

This study is a Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial in China. Patients who have HER2-positive MBC and have not received chemotherapy or biologic therapy (including approved or investigational tyrosine kinase/HER inhibitors or

vaccines) for their metastatic disease are eligible for the study. Patients who have received one prior hormonal treatment for MBC are eligible. Patients may have received systemic breast cancer treatment in the neoadjuvant or adjuvant setting, provided that the patient experienced a disease–free interval (DFI) of ≥ 12 months from completion of systemic treatment (excluding hormonal therapy) to metastatic diagnosis. Patients may have received Herceptin and/or a taxane in the neoadjuvant or adjuvant setting. HER2-positive status determined using archival, paraffin-embedded tumor tissue will be confirmed in a central laboratory by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH).

Number of Patients

A total of 240 patients will be randomized in a 1:1 ratio to one of two treatment arms

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form, obtained prior to any study procedure
- Age ≥ 18 years
- Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease that is suitable for chemotherapy

  Patients with measurable or nonmeasurable disease are eligible.

  Patients with only bone metastases are eligible provided that some bone metastases have not been previously irradiated and that tumor tissue samples from the primary tumor are available for central HER2 testing.

  Locally recurrent disease must not be amenable to resection with curative intent.
- HER2-positive MBC (defined as 3+ by IHC and/or ISH amplification ratio ≥ 2.0) confirmed by a Sponsor-designated central laboratory

  It is strongly recommended that a formalin–fixed paraffin–embedded (FFPE) tissue block from the primary tumor (or metastatic lesion if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility. However, if that is not possible, unstained and freshly cut slides need to be submitted (see Section 4.5.3 for further details). Tissue will subsequently be used for assessment of biomarkers.
- Left ventricular ejection fraction (LVEF) ≥ 55% at baseline (within 42 days prior to randomization) as determined by either echocardiography (ECHO) or multiple–gated acquisition (MUGA) scan (ECHO is the preferred method)

  If the patient is randomized, the same method of LVEF assessment, ECHO or MUGA, must be used throughout the study, and to the extent possible, be obtained at the same institution (see Section 4.5.8). Any prestudy LVEF values obtained during and after Herceptin neoadjuvant or adjuvant treatment will be obtained, as applicable.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- For women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined nonhormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment (Herceptin and/or pertuzumab)

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, and certain non-hormonal intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide

- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment (Herceptin and/or pertuzumab)

    Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

    Negative serum pregnancy test in women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization.

    Able to comply with the study protocol, in the investigator's judgment

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of anticancer therapy for MBC, with the exception of one prior hormonal regimen for MBC, which must be stopped prior to randomization

    Anticancer therapy for MBC includes any epidermal growth factor receptor or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC.

    One prior hormonal regimen for MBC may include more than one hormonal therapy. If a patient is switched to a different hormonal therapy for reasons other than disease progression (e.g., toxicity or local standard practice), this will be counted as one regimen. If a patient is switched to a different hormonal therapy because of disease progression, this will be counted as two regimens, and the patient will not be eligible for the study.
- History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except Herceptin used in the neoadjuvant or adjuvant setting
- History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a DFI from completion of systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months
- History of persistent Grade ≥ 2 hematologic toxicity resulting from previous neoadjuvant or adjuvant therapy (all grades based on National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0 [NCI CTCAE v 4.0])
- Grade ≥ 3 peripheral neuropathy at randomization
- History of other malignancy within the previous 5 years, except for carcinoma in situ of the cervix or non-melanoma skin carcinoma that has been previously treated with curative intent
- Current clinical or radiographic evidence of CNS metastases

    A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain is mandatory within 28 days before randomization in cases of clinical suspicion of brain metastases.
- History of exposure to the following cumulative doses of anthracyclines:

    Doxorubicin or liposomal doxorubicin > 360 mg/m2

    Epirubicin > 720 mg/m2

    Mitoxantrone > 120 mg/m2 and idarubicin > 90 mg/m2

    Other anthracycline greater than the equivalent of 360 mg/m2 of doxorubicin

        If more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.
- Current uncontrolled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg) or unstable angina

- History of congestive heart failure of any New York Heart Association classification, or serious cardiac arrhythmia requiring treatment (excluding atrial fibrillation or paroxysmal supraventricular tachycardia)
- History of myocardial infarction within 6 months prior to randomization
- History of LVEF decrease to < 50% during or after prior Herceptin neoadjuvant or adjuvant therapy
- Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy
- Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization:

  Absolute neutrophil count < 1500 cells/μL

  Platelet count < 100,000 cells/μL

  Hemoglobin < 9 g/dL

  Total bilirubin greater than the upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)

  AST or ALT > 2.5 × ULN (> 5 × ULN in patients with liver metastases)

  AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum ALP > 2.5 × ULN

  Serum ALP may be > 2.5 × ULN only if bone metastases are present and AST and ALT are < 1.5 × ULN.

  Serum creatinine > 2.0 mg/dL or 177 μmol/L

  INR and aPTT or PTT > 1.5 × ULN (unless on therapeutic anti-coagulation)
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Pregnant or lactating or intending to become pregnant during the study
- Treatment with any investigational treatment within 28 days prior to randomization
- Current known infection with HIV, hepatitis C virus, or active hepatitis B virus (HBV)

  Patients who are known carriers of HBV may be included in the study. Active HBV is defined as presence of each of the following: positive test for hepatitis B surface antigen, detectable levels of HBV DNA, and ALT > ULN.
- Receipt of intravenous (IV) antibiotics for infection within 14 days prior to randomization
- Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent), excluding inhaled corticosteroids
- Known hypersensitivity to any of the protocol–specified study treatments
- Concurrent participation in an interventional or noninterventional study

Length of Study

A total of approximately 240 patients (approximately 120 per arm) will be enrolled. The recruitment period is estimated to be 15 months.

The primary analysis of PFS will be performed after 123 PFS events have occurred, and the required PFS events will be reached at approximately 23 months after the first patient is enrolled into the study.

End of Study

The end of the study *is defined as 3 years after the date when the last patient is enrolled (LPI), or when the last patient, last visit (LPLV) occurs, whichever occurs later.*

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v 1.1; Therasse et al. 2000), or death from any cause within 18 weeks after the final tumor assessment, whichever occurs first

  Assessments will be based on review of radiological images (e.g., MRI scans, CT scans, bone scans, chest X-rays), as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid) and photographic data, if available.

The secondary efficacy outcome measures for this study are as follows:

- OS, defined as the time from randomization to death from any cause
- Objective response, defined as a complete response or partial response that is confirmed 28–42 days later, as determined by the investigator using RECIST v 1.1
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v 1.1, or death from any cause, whichever occurs first

Exploratory Outcome Measures

The exploratory outcome measures for this study may include, but are not limited to, the following:

- Expression level of HER2/3 mRNA as measured by quantitative real-time polymerase chain reaction
- PIK3CA status (i.e., mutation not detected or mutation detected by PCR based mutational analyses or by other technologies suited for mutational analyses)
- Expression of PD-L1 and CD8 as assessed by IHC or by other suitable technologies

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence of symptomatic left ventricular systolic dysfunction
- Incidence of asymptomatic LVEF events
- LVEF measurements over the course of the study
- Incidence and severity of adverse events and serious adverse events NCI CTCAE v 4.0)
- Changes in clinical laboratory results during the study

Investigational Medicinal Products

Herceptin, pertuzumab, and placebo are investigational medicinal products in this study. Treatments will be administered on Day 1 of each specified cycle.

All patients will receive Herceptin by IV infusion in 3-week cycles, as follows:

Herceptin (8 mg/kg loading dose for Cycle 1, followed by 6 mg/kg for subsequent cycles)

Herceptin will be administered until disease progression or unacceptable toxicity.

Test Product

Patients in Arm B will receive pertuzumab (840 mg loading dose for Cycle 1, followed by 420 mg for subsequent cycles) by IV infusion every 3 weeks until disease progression or unacceptable toxicity.

Comparator

Patients in Arm A will receive placebo by IV infusion every 3 weeks until disease progression or unacceptable toxicity. *Note that upon approval of protocol YO29296 Version 4, placebo will no longer be administered to patients in Arm A who are still receiving study treatment.*

Non-Investigational Medicinal Products

Docetaxel is a non-investigational medicinal product in this study. Sites will obtain and utilize commercially available docetaxel. Treatments will be administered on Day 1 of each specified cycle.

All patients will receive docetaxel in 3-week cycles, as follows:

Docetaxel (75 mg/m^2)

Prior to completion of Cycle 6, docetaxel should be discontinued only for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

Statistical Methods

Primary Analysis

The primary analysis of PFS will be performed after 123 PFS events have occurred, and the required PFS events are expected to be reached at around 23 months.

Determination of Sample Size

To reliably determine the predefined consistency value, a simulation method was used to estimate the required sample size. A total of 240 patients randomized in a 1:1 ratio and 123 PFS events in the two treatment arms are required, providing an appropriate 83% probability of showing consistency.

The sample size estimation was based on the following assumptions:

- The median PFS is 11 months in the control arm, with a PFS hazard ratio of 0.68
- The recruitment period is estimated to be 15 months

Interim Analyses

No interim analysis of efficacy is planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
CHF	congestive heart failure
CR	complete response
CT	computed tomography
CVAD	central venous access device
DFI	disease-free interval
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ESF	Eligibility Screening Form
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
HBV	active hepatitis B virus
HER2	human epidermal growth factor receptor 2
ICH	International Council for Harmonization
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	Independent Review Facility
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice or Web–based response system
JVP	jugular venous pressure
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute/ Common Terminology Criteria for Adverse Events

Abbreviation	Definition
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PR	partial response
qRT-PCR	quantitative real-time polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SWFI	sterile water for injection
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer is the most frequently occurring cancer among women, with an estimated 1.4 million new cancer cases diagnosed worldwide in 2008. Breast cancer is the most frequent cause of cancer death in women in both developed and developing regions (Jemal et al. 2011), although the incidence varies around the world and is higher in developed regions (>80 cases per 100,000) compared with developing areas (<40 cases per 100,000) (Ferlay et al. 2010). In Asia, 528,927 new breast cancer cases were diagnosed in 2008 (Ferlay et al. 2010). In China, the incidence is increasing; nearly 170,000 new cases were reported in 2008, compared with 126,000 cases in 2002 (Ferlay et al. 2010). Additionally, breast cancer accounts for 16.81% of all female cancers in China. In 2009, the incidence of female breast cancer in China was 42.55 per 100,000. After standardizing by age, the incidence was 23.16 per 100,000 in China versus 28.99 per 100,000 in the rest of the world (Chinese Cancer Registry Annual Report 2012). Consequently, breast cancer has been identified as a priority for cancer prevention, early detection, and therapy in China (Ferlay et al. 2010).

Although the treatment of metastatic breast cancer (MBC) is usually palliative in intent, this malignancy readily responds to systemic agents, and prolongation of survival and symptom palliation are now possible with modern medical management. Systemic treatments are in continual evolution as more active chemotherapeutic agents become available and biological factors have been incorporated into treatment. There are many agents available for the treatment of MBC that are used singly or in combination, according to the clinical situation. The most active drugs are anthracyclines, taxanes, alkylating agents, and vinca alkaloids. Used as single agents, they produce response rates of 20%–80%; however, the rare complete responses are short lived, and progression of disease is almost inevitable (Bernard-Marty et al. 2003; Chung and Carlson 2003).

The introduction of paclitaxel and docetaxel in the 1990s led to additional improvements in the management of MBC. The now common use of anthracyclines in the adjuvant treatment of early breast cancer has both increased the incidence of anthracycline-resistant MBC and restricted the use of anthracyclines in later stages of the disease, in order to avoid dose-limiting toxicity. There is also an increasing trend toward using taxanes earlier in the management of MBC in patients with no or minimal prior anthracycline exposure or in combination with anthracyclines or both.

With the growing understanding of the biology of breast cancer, multiple new targets for anticancer therapies are being identified. Trastuzumab (Herceptin®), which targets human epidermal growth factor receptor 2 (HER2), is globally approved for use as monotherapy or in combination with chemotherapy in the metastatic setting and in combination with chemotherapy as adjuvant treatment for HER2-positive breast cancer In China, in the adjuvant setting, Herceptin is approved for use as a single agent for the

adjuvant treatment of HER2-overexpressing breast cancer in patients who have received surgery and anthracycline-based chemotherapy and radiotherapy. The optimal management of MBC now takes into account not only a patient's general condition, medical history, tumor burden, and receptor status, but also the patient's HER2 status. Pertuzumab (Perjeta®), a recombinant humanized monoclonal antibody, binds to the dimerization epitope of HER2, thereby inhibiting dimerization of HER2 to other HER family members (HER1, HER3, and HER4). The combination of pertuzumab and Herceptin provides more complete HER pathway blockade because of their complementary modes of action (Baselga et al. 2012; Swain et al. 2013).

There is a significant need in China for new agents with novel mechanisms of action and non-overlapping toxicity that can be combined with established treatments for breast cancer.

1.2 HUMAN EPIDERMAL GROWTH FACTOR RECEPTORS

Evidence suggests that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. The HER tyrosine kinase receptor family is composed of four receptors: HER1 (epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4, these receptors mediate tumor cell growth, survival, and differentiation (Sundaresan et al. 1999; Yarden and Sliwkowski 2001). HER receptors normally exist as inactive monomers. Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation. Overexpression of HER2 is observed in 15%−20% of primary breast cancer (Chia et al. 2008; Ross et al. 2009; Pathmanathan et al. 2012; Bilous et al. 2012). In China, the number of patients recruited into this prospective multicenter study to investigate the expression of the HER2 in human breast carcinomas by comparing the concordance between immunohistochemistry (IHC) staining and fluorescence in situ hybridization (FISH) that were HER2 positive (2+ or 3+) was 42.6% (1342 of 3149) as detected by FISH and 46.9% (1477 of 3149) as detected by IHC. Overall, the authors concluded that there was good correlation between IHC and FISH in demonstrating HER2/neu overexpression and gene amplification (Xiao hong 2010). Several lines of scientific and clinical evidence support a direct role for HER2 overexpression in aggressive growth and poor prognosis (Slamon et al. 1987).

HER2 and HER3 have unique characteristics compared with HER1 and HER4. HER2 has no known ligand and in a state of overexpression can form active homodimers and initiate tyrosine kinase signaling without ligand stimulation. Additionally, as HER2 concentrations increase, the incidence of HER2 interactions with other receptors is also increased, resulting in a broad recruitment of a number of proteins (Jones et al. 2006). Recent data obtained using microarray technology suggest that the HER2 receptor can bind to more than 17 different proteins and may recruit

proteins that other HER receptors cannot recruit. These activities highlight the promiscuity of HER2 in its ability to bind to other HER receptors and initiate tyrosine kinase signaling through several mechanisms (Jones et al. 2006). HER3 differs from the other HER receptors in that it has no intracellular tyrosine kinase domain and cannot initiate cellular signaling without binding to either HER1, HER2, or HER4 (Guy et al. 1994). The prognostic significance of HER3 in breast cancer is controversial, because HER3 expression has been associated with both poor and favorable prognosis (Pawlowski et al. 2000; Bieche et al. 2003; Witton et al. 2003).

HER2 is thought to be the preferred partner for HER3 dimerization because it exists in an open configuration, mimicking a ligand-bound state (Sliwkowski 2003). In vitro data involving multiple HER2-positive cell lines have demonstrated higher mRNA levels of HER3 versus EGFR, suggesting that the HER2-HER3 interaction may represent a potent stimulus for tyrosine kinase signal transduction. These data support the hypothesis that the HER2-HER3 pair is the most transforming heterodimer and is the most mitogenic compared with other heterodimer pairs (Jones et al. 2006).

HER2 has emerged as an important prognostic and potential predictive factor in breast cancer. In the laboratory, HER2 overexpression results in oncogenic transformation and more aggressive tumor behavior. Despite associations with other known negative prognostic factors, HER2 overexpression has been independently associated with poorer disease-free survival and overall survival (OS) compared with tumors that do not overexpress HER2 (Pauletti et al. 2000).

1.3 BACKGROUND ON TREATMENTS

1.3.1 Herceptin

Herceptin, a humanized monoclonal antibody directed at the HER2 receptor, is indicated for the treatment of patients with HER2-positive breast cancer both in the adjuvant treatment setting and in the metastatic treatment setting. The addition of Herceptin to standard chemotherapy prolongs time to progressive disease, or progression-free survival (PFS), and improves survival when given with chemotherapy to women with HER2-positive breast cancer (Slamon et al. 2001; Romond et al. 2005).

Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, graded 3+ by IHC, and/or with HER2 gene amplification, as determined by FISH. In an evaluation of tissue from patients who participated in a randomized Phase III study of chemotherapy plus Herceptin versus chemotherapy alone (Slamon et al. 2001), as measured by relative risk for time to disease progression, patients treated with Herceptin plus chemotherapy achieved greater benefit if they had HER2 assay results of 3+ by IHC (relative risk: 0.42; 95% CI: 0.33, 0.54) or FISH positive (relative risk: 0.44; 95% CI: 0.34, 0.57), compared with HER2 assay results of IHC 2+ (relative risk: 0.76; 95% CI: 0.5, 1.15) or IHC 2+ and FISH positive (relative risk: 0.54; 95% CI: 0.21, 1.35) (Herceptin® U.S. Package Insert, November 2006).

A Phase II randomized study evaluated Herceptin and docetaxel versus docetaxel alone as a first-line treatment for HER2-positive MBC (Marty et al. 2005). A total of 186 patients received at least one dose of protocol therapy. The addition of Herceptin to 100 mg/m^2 docetaxel for at least six cycles resulted in superior clinical efficacy with improved overall response rates (61% vs. 34%; p = 0.0002), OS (median, 31.2 months vs. 22.7 months; p = 0.0325), time to progressive disease (median, 11.7 months vs. 6.1 months; p = 0.0001), time to treatment failure (median, 9.8 months vs. 5.3 months; p = 0.0001), and duration of response (median, 11.7 months vs. 5.7 months; p = 0.009). There was little difference in the number and severity of adverse events (AEs) between the treatment arms. Grade 3 or 4 neutropenia was seen more commonly with combination treatment (32%) than with docetaxel alone (22%), and there was a slightly higher incidence of febrile neutropenia in the combination arm (23% vs. 17%, respectively). More patients in the combination arm had decreases in left ventricular ejection fraction (LVEF) compared with the docetaxel-alone arm (17% vs. 8%, respectively), and 1 (1%) patient in the combination arm experienced symptomatic heart failure. An additional patient in the combination arm experienced congestive heart failure (CHF) after discontinuation of study treatment and during treatment with an investigational anthracycline. The CHF event in this second patient was assessed by the investigator as related to the investigational anthracycline (Marty et al. 2005). A Phase III, randomized, multicenter, double-blind, placebo-controlled trial, Study WO20698/TOC4129g (CLEOPATRA), is of 808 patients with HER2-positive MBC, in which patients were randomized in a 1:1 ratio to receive either placebo in combination with Herceptin plus docetaxel or pertuzumab in combination with Herceptin plus docetaxel. This data is presented below in Section 1.3.2.2.

Herceptin is well tolerated both as a single agent and in combination with standard chemotherapy for breast cancer (Cobleigh et al. 1998; Slamon et al. 2001). The most significant AE observed in patients who receive Herceptin is cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic CHF. Risk factors for cardiac failure in the setting of Herceptin treatment include co-administration with anthracycline–based chemotherapy, increasing age, a decreasing LVEF during treatment to below the lower limit of normal (LLN), and the use of anti-hypertensive medications (Tan-Chiu et al. 2005).

1.3.2 Pertuzumab

Pertuzumab is a fully humanized monoclonal antibody based on the human IgG1 (κ) framework sequences and consisting of two heavy chains (449 residues) and two light chains (214 residues). Like Herceptin, pertuzumab is directed against the extracellular domain of HER2. However, it differs from Herceptin in the epitope–binding regions of the light chain (12–amino acid difference) and heavy chain (29–amino acid difference). As a result, pertuzumab binds to an epitope within what is known as subdomain 2 of HER2 whereas the epitope for Herceptin is localized to subdomain 4 (Cho et al. 2003; Franklin et al. 2004).

Pertuzumab acts by blocking the association of HER2 with other HER family members, including HER1 (EGFR), HER3, and HER4. As a result, pertuzumab inhibits ligand–initiated intracellular signaling through two major signal pathways: MAP kinase and PI3 kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis, respectively (Hanahan and Weinberg 2000).

Recent data from a clinical trial of lapatinib supports the hypothesis that HER2 plays an active role in tumor biology even with the administration of Herceptin (Geyer et al. 2006). These data suggest that a broader blockade of HER2 through interruption of heterodimerization may provide clinical benefit.

Both pertuzumab and Herceptin target the HER2 receptor but bind at distinct epitopes on the receptor, with different modes of action, including ADCC (antibody dependent cellular cytotoxicity, inhibition of downstream signaling, and inhibition of receptor heterodimerization).

1.3.2.1 Phase I and II Clinical Studies in Solid Tumors

Pertuzumab has been studied in several Phase I and II clinical trials in solid tumors, including breast, prostate, ovarian, and lung cancer. Pertuzumab was given until evidence of progressive disease or toxicity.

AEs reported in trials of single-agent pertuzumab ($n = 353$) were commonly Grade 1 or 2 in severity and included diarrhea (58%), fatigue (32%), nausea (31%), abdominal pain (24%), vomiting (22%), anorexia (19%), and rash (17%). Grade 3 or 4 AEs were less frequently reported, with the more frequent events including Grade 3 diarrhea (7%), Grade 3 vomiting (5%), and Grade 3 nausea (4%). Decreases in LVEF were reported in 14% of patients. LVEF decreases of ≥ 10 percentage points to an LVEF of $< 50\%$ were reported in 21 of 203 patients (10%) who had a baseline LVEF and at least one post–baseline LVEF assessment.

Overall, CHF has been observed in 3 patients. One patient with symptomatic Grade 3 cardiac dysfunction received pertuzumab plus Herceptin for relapsed HER2-positive MBC, another patient received pertuzumab plus gemcitabine for platinum refractory ovarian cancer, and the third patient received pertuzumab as a single agent for HER2-negative MBC.

Pertuzumab has been evaluated in Phase II studies in combination with Herceptin in patients with HER2-positive MBC who have previously received Herceptin for metastatic disease. One study, conducted by the National Cancer Institute (NCI), enrolled 11 patients with previously treated HER2-positive MBC. Two of the 11 patients exhibited a partial response (PR) (Portera et al. 2008). In the second study, BO17929, 66 patients who had previously been treated with Herceptin for HER2-positive MBC received the combination of pertuzumab and Herceptin every 3 weeks until disease progression. In a preliminary analysis of 42 of the 66 patients, 1 patient had a complete response (CR),

5 patients had a PR, and 17 patients had stable disease (SD) of at least two cycles in duration (Baselga et al. 2007).

1.3.2.2 Phase III Clinical Study in Metastatic Breast Cancer

CLEOPATRA is a Phase III, randomized, multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive MBC, in which patients were randomized in a 1:1 ratio to receive either placebo in combination with Herceptin plus docetaxel or pertuzumab in combination with Herceptin plus docetaxel.

The primary endpoint of this randomized trial was PFS as assessed by an independent review facility (IRF). The results from this randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab group compared with the placebo group (hazard ratio: 0.62; 95% CI: 0.51, 0.75; $p < 0.0001$) and an increase in median PFS of 6.1 months (18.5 months in the pertuzumab group versus 12.4 months in the placebo group) (Baselga et al. 2012). CLEOPATRA Study has also shown a statistically significant improvement in OS for the pertuzumab group (hazard ratio: 0.68; 95% CI: 0.56, 0.84; $p \leq 0.001$). The median OS was 56.5 months in the pertuzumab group compared to 40.8 months in the control group (Swain et al. 2015).

In CLEOPATRA, the addition of pertuzumab to Herceptin did not increase the rates of symptomatic or asymptomatic cardiac dysfunction. A low level of cardiac toxicities, predominantly asymptomatic declines in LVEF have been reported in both arms in CLEOPATRA. The most frequently reported cardiac-related AE was left ventricular systolic dysfunction (LVSD), with a total of 34 patients [8.6%] in the Pla + T + D arm versus 22 patients [5.4%] in the Ptz + T + D arm). AEs (any grade) of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin were reported more frequently in the pertuzumab group than in the placebo group. The events were mostly Grade 1 or 2 and occurred during the period of concomitant docetaxel administration. Compared with the placebo group, the pertuzumab group had an increased incidence of Grade ≥ 3 or worse febrile neutropenia (13.8% vs. 7.6%, respectively) and diarrhea (7.9% vs. 5%, respectively).

1.3.3 Docetaxel

Docetaxel is an anti-neoplastic agent that binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, blocking cells in the M-phase of the cell cycle and leading to cell death. Extensive Phase II and III data have led to regulatory approvals for docetaxel use either in combination or as monotherapy for the treatment of breast cancer. For further information on the efficacy, safety, and pharmacokinetics of docetaxel, please refer to the currently approved prescribing information.

1.4 RATIONALE FOR THE STUDY

Pertuzumab represents a new anti-HER2 agent with a novel mechanism of action targeting inhibition of HER2 dimerization. Nonclinical and clinical data generated to date suggest that pertuzumab may provide broader HER2 blockade through inhibition of HER2 homo- and heterodimerization. Pertuzumab has been shown in both nonclinical and clinical experiments to have superior antitumor effects when combined with other anti-HER2 treatments such as Herceptin.

Pertuzumab is already approved in many countries (including the United States, the European Union, Japan, the Republic of Korea, and Taiwan) for use in combination with Herceptin plus docetaxel for the treatment of patients with HER2-positive MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The pertuzumab treatment effect is unlikely to be sensitive to ethnic factors because of its mechanism of action, the biological similarities in HER2-positive disease throughout the world, and similarities in medical practice between Asian and Western countries. Nevertheless, the safety and efficacy of pertuzumab treatment in Chinese patients with MBC will be evaluated in this study.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of pertuzumab plus Herceptin plus docetaxel compared with placebo plus Herceptin plus docetaxel in patients with previously untreated HER2-positive MBC, as measured by investigator-assessed PFS

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To compare OS between the two treatment arms
- To compare the objective response rate (ORR) between the two treatment arms
- To compare the duration of objective response between the two treatment arms

2.1.3 Exploratory Objective

The exploratory objective for this study is as follows:

- To explore the relationship of biomarkers, such as PI3K status, HER2/3 mRNA, PD-L1, and CD8 expression, with efficacy (response rate, PFS, and OS)

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To compare the safety profile between the two treatment arms *(including crossover patients and those no longer receiving placebo)*

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial in China. Patients who have HER2-positive MBC and have not received chemotherapy or biologic therapy (including approved or investigational tyrosine kinase/HER inhibitors or vaccines) for their metastatic disease are eligible for the study. Patients who have received one prior hormonal treatment for MBC are eligible. Patients may have received systemic breast cancer treatment in the neoadjuvant or adjuvant setting, provided that the patient experienced a disease–free interval (DFI) of $\geq$ 12 months from completion of systemic treatment (excluding hormonal therapy) to metastatic diagnosis. Patients may have received Herceptin and/or a taxane in the neoadjuvant or adjuvant setting. HER2-positive status determined using archival, paraffin-embedded tumor tissue will be confirmed in a central laboratory by IHC and/or FISH.

A total of 240 patients will be randomized in a 1:1 ratio to one of two treatment arms:

Arm A

- Placebo, administered by intravenous (IV) infusion every 3 weeks until disease progression or unacceptable toxicity
- Herceptin (8 mg/kg loading dose for Cycle 1, followed by 6 mg/kg for subsequent cycles), administered by IV infusion every 3 weeks until disease progression or unacceptable toxicity
- Docetaxel (75 mg/m^2), administered by IV infusion every 3 weeks

  Prior to completion of Cycle 6, docetaxel should be discontinued only for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

Arm B

- Pertuzumab (840-mg loading dose for Cycle 1, followed by 420 mg for subsequent cycles), administered by IV infusion every 3 weeks until disease progression or unacceptable toxicity
- Herceptin (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for subsequent cycles), administered by IV infusion every 3 weeks until disease progression or unacceptable toxicity
- Docetaxel (75-mg/m^2), administered by IV infusion every 3 weeks

  Prior to completion of Cycle 6, docetaxel should only be discontinued for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

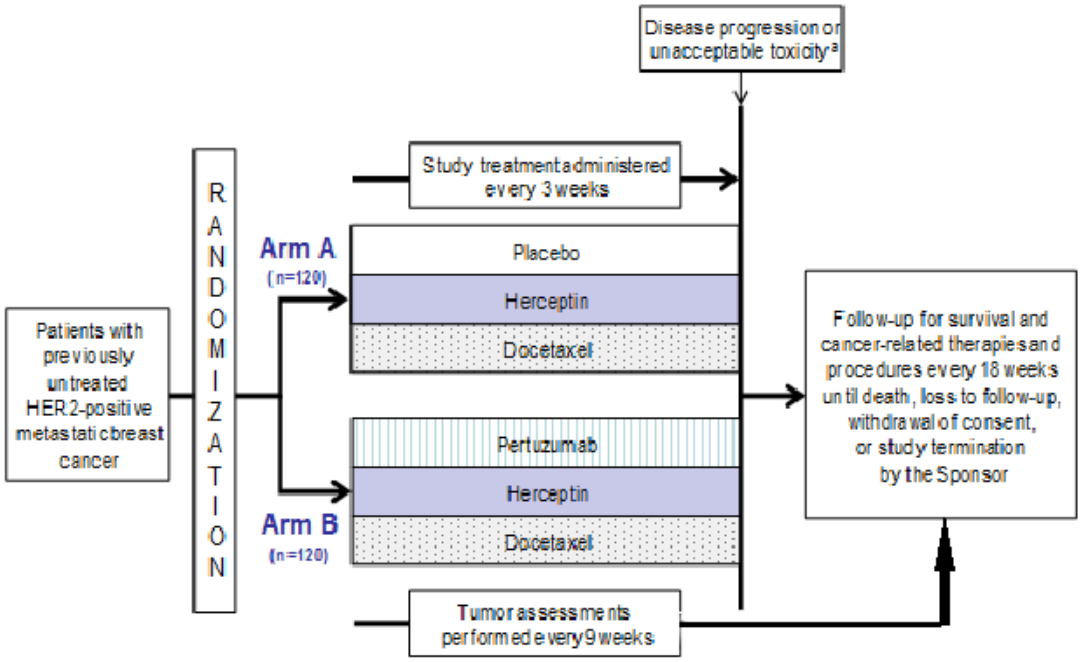
Study treatment will be discontinued at the time of disease progression or unacceptable toxicity, with the possible exception of docetaxel, as described above. Tumor assessments will be performed *as per local clinical practice*, regardless of treatment delays, until disease progression (see Figure 1).

At the primary analysis (2018), clinically meaningful improvement in the primary efficacy endpoint of investigator-assessed PFS was demonstrated. As a result, upon approval of protocol YO29296 Version 4, patients in Arm A who are still receiving study treatment will be offered the option to cross over and receive pertuzumab (in place of placebo) in addition to Herceptin and docetaxel until disease progression or unacceptable toxicity. For patients in Arm A who do not choose the crossover option, placebo will be discontinued and study treatment with Herceptin and docetaxel will continue until disease progression or unacceptable toxicity.

Patients who are still receiving study treatment at the time of the end of this study will continue to be offered study treatment until disease progression or unacceptable toxicity. Patients may receive pertuzumab as part of an open-label extension (OLE) Study MO29406, if eligible (see Section 3.1.1). Criteria for continued access to Roche IMPs after the end of Study YO29296 are provided in Section 4.3.4.

After discontinuation of study treatment, information on survival and cancer-related therapies and medical or surgical procedures will be collected by telephone every 18 weeks until the end of the study, death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment. The study design is presented graphically in Figure 1. A schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



HER2 = human epidermal growth factor receptor 2.

Note: Upon approval of protocol YO29296 Version 4, tumor assessments will be performed as per local clinical practice.

[a] Prior to completion of Cycle 6, docetaxel should be discontinued only for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

3.1.1 *Open-Label Extension Study MO29406*

Patients may have the opportunity to continue treatment with pertuzumab as part of OLE Study MO29406, if protocol-defined criteria are met (see Section 4.3.4).

3.1.2 Interim Analyses

No interim analysis of efficacy is planned.

3.2 END OF STUDY

The end of the study *is defined as 3 years after the date when the last patient is enrolled (LPI), or when the last patient, last visit (LPLV) occurs, whichever occurs later.*

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Including Patients Who Have Received Prior Hormonal Treatment for Metastatic Breast Cancer

Patients who have received one prior hormonal treatment for MBC will be eligible for this trial. The results of a randomized, controlled study suggested that prior hormonal treatments did not appear to have a significant effect on the benefit of Herceptin (Slamon et al. 2001). Approximately 25% of all enrolled patients had received prior hormonal therapy in the MBC treatment setting. Efficacy gains were similar in patients with tumors that were estrogen receptor (ER) or progesterone receptor (PgR) positive, or both.

3.3.2 Rationale for Using the Combination of Herceptin and Docetaxel for Patients with HER2-Positive Metastatic Breast Cancer

Currently, there is no single chemotherapy regimen that can be considered the global standard of care for MBC. However, on the basis of positive results from two large, pivotal trials (Studies H0648g and M77001), the combination of Herceptin with a taxane is now established as a first-line treatment of choice for patients with HER2-positive MBC (Slamon et al. 2001; Marty et al. 2005).

The objectives of Study H0648g were to evaluate the efficacy and safety of Herceptin in combination with first-line chemotherapy regimens, including paclitaxel. The study enrolled 469 patients. The results of Study H0648g demonstrated that the combination of Herceptin and paclitaxel significantly prolonged the time to progressive disease compared with paclitaxel alone (median, 7.4 months versus 4.6 months; $p < 0.001$). Patients treated with Herceptin and paclitaxel had an increased response rate (50% versus 32%; $p < 0.001$) and an improved OS (median, 25.1 months versus 20.3 months; $p = 0.046$) compared with paclitaxel alone (Slamon et al. 2001).

Similar results were obtained in a randomized, multicenter trial (Study M77001) of Herceptin combined with docetaxel versus docetaxel alone, as first-line therapy for HER2–overexpressing MBC (Marty et al. 2005), as detailed in Section 1.1.

3.3.3 Rationale for Using the Combination of Herceptin, Pertuzumab, and Docetaxel for Patients with HER2-Positive Metastatic Breast Cancer

Pertuzumab, a recombinant humanized monoclonal antibody to the HER2 receptor, exerts its activity by inhibiting HER2 homo- and heterodimerization. Herceptin, another humanized monoclonal antibody to the HER2 receptor, blocks HER2 signaling pathways when HER2 is overexpressed on breast tumor cells. These two monoclonal antibodies bind to distinct epitopes on the HER2 receptor without competing with each other, resulting in two distinct mechanisms for disrupting HER2 signaling. These mechanisms are complementary and result in augmented therapeutic efficacy when pertuzumab and Herceptin are given in combination.

Nonclinical data suggest at least additive efficacy when the two agents are administered together, resulting in significantly reduced tumor volume compared with either agent alone. Clinically, pertuzumab may have optimal therapeutic effects when given in combination with Herceptin to patients with HER2-positive cancers, as evidenced by data generated in a Phase II study of patients with previously treated HER2-positive MBC (Baselga et al. 2007) and confirmed by data from a Phase III, global, multicenter CLEOPATRA (Swain et al. 2013).

In this study, docetaxel will be included in the standard treatment plan, because it has been proven efficacious when combined with Herceptin in women with HER2-positive MBC and should provide clinical benefit independent of pertuzumab.

3.3.4 Rationale for Dosage Selection of Pertuzumab, Herceptin, and Docetaxel

The dose of pertuzumab was based on pharmacokinetic (PK) studies demonstrating similar pharmacokinetics observed across doses with a range or 2.0-15.0 mg/kg (140 mg-1050 mg for a 70-kg patient) (Agus et al. 2005). A two-compartment model adequately described the concentration-time data, with a systemic serum clearance of approximately 0.24 L/day and a terminal half-life of approximately 17 days for a typical patient. On the basis of these data, a dosing interval of 3 weeks is recommended in clinical studies. In the Phase II studies, a loading dose of 840 mg (followed by 420 mg every 3 weeks) was capable of attaining steady-state trough and peak concentrations by the second cycle. Population PK modeling of data from Phase Ia and Phase II studies supports the continued use of fixed, non–weight-based dosing in female patients (Ng et al. 2006). Additionally, there was no evidence of an impact of pertuzumab on the pharmacokinetics of co-administered chemotherapeutic agents docetaxel and capecitabine in Phase Ib studies.

One study, that evaluated docetaxel in doses of 60, 75, or 100 mg/m^2, demonstrated similar PFS and OS outcomes between patients who received docetaxel 75 mg/m^2 and patients who received docetaxel 100 mg/m^2, suggesting that either dose may be effective (Harvey et al. 2006). The study also demonstrated a dose–toxicity effect with respect to myelosuppression and the incidence of febrile neutropenia. Therefore, docetaxel 75 mg/m^2 IV every 3 weeks may be equally efficacious with a more favorable safety profile compared with docetaxel 100 mg/m^2 IV every 3 weeks. Given the prior safety experience with docetaxel and pertuzumab, and the recognized risk of Grade 3 or 4 neutropenia or febrile neutropenia with Herceptin plus docetaxel, the docetaxel dose employed in this trial will be 75 mg/m^2. Safety data are available for Herceptin given every 3 weeks (8-mg/kg loading dose, followed by 6-mg/kg for subsequent doses), either alone (Study WO16229) or with paclitaxel (Study BO15935). These data suggest that there is no clinically important difference in the safety profile when Herceptin is given every 3 weeks versus every week (i.e., according to the approved schedule).

3.3.5 Rationale for Exploratory Biomarker Analyses

Within CLEOPATRA a panel of biomarkers have been assessed to explore a potential prognostic and predictive value. While no predictive value could be determined for any of the markers tested, a strong prognostic impact was observed for PIK3CA status with patients whose tumors carried a PIK3CA mutation showing significantly poorer prognosis compared to patients whose tumors were tested wild type for PIK3CA (Baselga et al. 2012). A similar but less strong effect was observed for HER2 mRNA levels. As the number of Chinese patients in WO20698 was very small, it is planned to explore these two markers PIK3CA and HER2/3 mRNA in this study to explore the incidence of PIK3CA mutation and the levels of HER2/3 mRNA in the Chinese population and the potential value as prognostic and/or predictive markers.

With the evolving field of cancer immunotherapy and newly emerging data on association of immune markers in response to HER2 targeted therapy, PD-L1 and CD8 may be assessed as well, if tissue availability allows for it. This may allow exploration of the impact of PD-L1 expression on outcome, as well as relationship of degree of infiltration of tumor and stromal tissue by cytotoxic T-cells, as assessed by CD8 IHC staining.

Additional markers may be assessed based on tissue availability and scientific interest and requirement.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v 1.1; Therasse et al. 2000), or death from any cause within 18 weeks after the final tumor assessment, whichever occurs first

  Assessments will be based on review of radiological images (e.g., magnetic resonance imaging [MRI] scans, computed tomography [CT] scans, bone scans, chest X-rays), as well as cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid) and photographic data, if available.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- OS, defined as the time from randomization to death from any cause
- Objective response, defined as a CR or PR that is confirmed 28–42 days later, as determined by the investigator using RECIST v 1.1
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v 1.1, or death from any cause, whichever occurs first

3.4.1.3 Exploratory Efficacy Outcome Measures

The exploratory outcome measures for this study may include, but are not limited to, the following:

- Expression level of HER2/3 mRNA as measured by quantitative real-time polymerase chain reaction (qRT-PCR)
- PIK3CA status(i.e., mutation not detected or mutation detected by PCR based mutational analyses or by other technologies suited for mutational analyses)
- Expression of PD-L1 and CD8 as assessed by IHC or by other suitable technologies

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence of symptomatic LVSD
- Incidence of asymptomatic LVEF events
- LVEF measurements over the course of the study
- Incidence and severity of AEs and serious adverse events (SAEs) based on National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0 (NCI CTCAE v 4.0)
- Changes in clinical laboratory results during the study

4. MATERIALS AND METHODS

4.1 PATIENTS

The study population for this trial is patients with HER2-positive MBC who have not been previously treated with chemotherapy and/or biologic therapy for their MBC. Patients with Stage IV disease at initial disease presentation as well as those who have progressed following either neoadjuvant or adjuvant therapy with a DFI of $\geq$12 months will be included, and they may have received Herceptin and/or taxanes in the neoadjuvant or adjuvant setting.

4.1.1 Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for study entry:

- Signed Informed Consent Form, obtained prior to any study procedure
- Age $\geq$18 years
- Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease that is suitable for chemotherapy

  Patients with measurable or nonmeasurable disease are eligible.

  Patients with only bone metastases are eligible provided that some bone metastases have not been previously irradiated and that tumor tissue samples from the primary tumor are available for central HER2 testing.

  Locally recurrent disease must not be amenable to resection with curative intent.

- HER2-positive MBC (defined as 3+ by IHC and/or ISH amplification ratio ≥2.0) confirmed by a Sponsor-designated central laboratory

  It is strongly recommended that a formalin–fixed paraffin–embedded (FFPE) tissue block from the primary tumor (or metastatic lesion if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility. However, if that is not possible, unstained and freshly cut slides need to be submitted (see Section 4.5.3 for further details). Tissue will subsequently be used for assessment of biomarkers.

- LVEF ≥55% at baseline (within 42 days prior to randomization) as determined by either echocardiography (ECHO) or multiple–gated acquisition (MUGA) scan (ECHO is the preferred method)

  If the patient is randomized, the same method of LVEF assessment, ECHO or MUGA, must be used throughout the study, and to the extent possible, be obtained at the same institution (see Section 4.5.8). Any prestudy LVEF values obtained during and after Herceptin neoadjuvant or adjuvant treatment will be obtained, as applicable.

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

- For women who are not postmenopausal (postmenopausal defined as ≥12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined nonhormonal contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of study treatment (Herceptin and/or pertuzumab)

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, and certain non-hormonal intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide

- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last dose of study treatment (Herceptin and/or pertuzumab)

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Negative serum pregnancy test in women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization.
- Able to comply with the study protocol, in the investigator's judgment

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of anticancer therapy for MBC, with the exception of one prior hormonal regimen for MBC, which must be stopped prior to randomization

  Anticancer therapy for MBC includes any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC.

  One prior hormonal regimen for MBC may include more than one hormonal therapy. If a patient is switched to a different hormonal therapy for reasons other than disease progression (e.g., toxicity or local standard practice), this will be counted as one regimen. If a patient is switched to a different hormonal therapy because of disease progression, this will be counted as two regimens, and the patient will not be eligible for the study.
- History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except Herceptin used in the neoadjuvant or adjuvant setting
- History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a DFI from completion of systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months
- History of persistent Grade ≥ 2 hematologic toxicity resulting from previous neoadjuvant or adjuvant therapy (all grades based on NCI CTCAE v 4.0)
- Grade ≥ 3 peripheral neuropathy at randomization
- History of other malignancy within the previous 5 years, except for carcinoma in situ of the cervix or non-melanoma skin carcinoma that has been previously treated with curative intent
- Current clinical or radiographic evidence of CNS metastases

  A CT or MRI scan of the brain is mandatory within 28 days before randomization in cases of clinical suspicion of brain metastases.
- History of exposure to the following cumulative doses of anthracyclines:

  Doxorubicin or liposomal doxorubicin $>$ 360 mg/m2

  Epirubicin $>$ 720 mg/m2

  Mitoxantrone $>$ 120 mg/m2 and idarubicin $>$ 90 mg/m2

  Other anthracycline greater than the equivalent of 360 mg/m2 of doxorubicin

  If more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.

- Current uncontrolled hypertension (systolic blood pressure $>$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg) or unstable angina
- History of CHF of any New York Heart Association (NYHA) classification, or serious cardiac arrhythmia requiring treatment (excluding atrial fibrillation or paroxysmal supraventricular tachycardia)
- History of myocardial infarction within 6 months prior to randomization
- History of LVEF decrease to $<$ 50% during or after prior Herceptin neoadjuvant or adjuvant therapy
- Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy
- Inadequate organ function, evidenced by the following laboratory results within 28 days prior to randomization:

  Absolute neutrophil count $<$ 1500 cells/μL

  Platelet count $<$ 100,000 cells/μL

  Hemoglobin $<$ 9 g/dL

  Total bilirubin greater than the upper limit of normal (ULN) (unless the patient has documented Gilbert's syndrome)

  AST or ALT $>$ 2.5 $\times$ ULN ($>$ 5 $\times$ ULN in patients with liver metastases)

  AST (SGOT) or ALT (SGPT) $>$ 1.5 $\times$ ULN with concurrent serum ALP $>$ 2.5 $\times$ ULN

    Serum ALP may be $>$ 2.5 $\times$ ULN only if bone metastases are present and AST and ALT are $<$ 1.5 $\times$ ULN.

  Serum creatinine $>$ 2.0 mg/dL or 177 μmol/L

  INR and aPTT or PTT $>$ 1.5 $\times$ ULN (unless on therapeutic anti-coagulation)

  Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Pregnant or lactating or intending to become pregnant during the study
- Treatment with any investigational treatment within 28 days prior to randomization
- Current known infection with HIV, hepatitis C virus, or active hepatitis B virus (HBV)

  Patients who are known carriers of HBV may be included in the study. Active HBV is defined as presence of each of the following: positive test for hepatitis B surface antigen, detectable levels of HBV DNA, and ALT $>$ ULN.
- Receipt of IV antibiotics for infection within 14 days prior to randomization

- Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent), excluding inhaled corticosteroids
- Known hypersensitivity to any of the protocol–specified study treatments
- Concurrent participation in an interventional or noninterventional study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

A total of approximately 240 patients (approximately 120 per treatment arm) will be enrolled from approximately 20 sites in China. An interactive voice or Web–based response system (IxRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.

A permuted block randomization scheme will be applied to achieve balance in treatment assignment within each of four strata: disease type (visceral disease vs. non-visceral disease) and hormone receptor status (ER and PgR negative or ER and/or PgR positive). Non-visceral disease will include tumors located in the breast, bone, bone marrow, lymph nodes, skin and soft tissue. All other locations will be classed as visceral disease. Patients with tumors in multiple locations that cover both visceral and non-visceral disease (e.g., a patient with a tumor in the liver and bone lesions) will be classed as having "visceral disease" for the purposes of the analysis.

Treatment unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the patient's care by the investigator or a regulatory body. In general, unblinding of participant's treatment assignment during the conduct of the clinical study is not allowed unless there are compelling medical or safety reasons. If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by accessing the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

Unblinding will occur for Sponsor personnel involved in analyzing, reporting, and submitting the results of the primary analysis to regulatory authorities.

Upon approval of protocol YO29296 Version 4, the treatment assignment of patients in Arm A who are still on study treatment will be unblinded, allowing the investigators to present those patients with the option to cross over and receive pertuzumab (in place of placebo) in addition to Herceptin and docetaxel.

4.3 STUDY TREATMENT

Eligible patients will be treated in 3-week cycles with placebo, Herceptin, and docetaxel (Arm A) or pertuzumab, Herceptin, and docetaxel (Arm B). Patients will receive pertuzumab and Herceptin until disease progression or unacceptable toxicity. Prior to completion of Cycle 6, docetaxel should be discontinued only for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Pertuzumab and Placebo

Pertuzumab and placebo will be supplied by F. Hoffmann-La Roche (the Sponsor) and will be labeled according to the regulatory requirements in China and the International Conference of Harmonization (ICH) guideline for Good Clinical Practice. *Note that upon approval of protocol YO29296 Version 4, placebo will no longer be administered to patients in Arm A who are still receiving study treatment (see Section 3.1).*

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-cc vial contains approximately 420 mg of pertuzumab (14.0 mL/vial). Pertuzumab for use in China is intended only in clinical trials.

The formulation for placebo is equivalent to that for pertuzumab, without the active agent.

Vials of pertuzumab and placebo will be shipped at a temperature of 2°C–8°C (36°F–46°F), must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity, and should remain refrigerated until immediately prior to use. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. If a temperature deviation from the allowed 2°C–8°C is found during shipment or storage, contact the Sponsor to determine whether the drug is still appropriate for use.

DO NOT FREEZE and DO NOT SHAKE the pertuzumab (or placebo) vials. Store all vials within the outer carton, and protect them from light.

The medication must not be used beyond the expiration date stamped on the outer carton.

Because the pertuzumab (or placebo) formulation does not contain a preservative, the vial seal may be punctured only once. Any remaining solution should be discarded.

Appropriate aseptic techniques should be used. Pertuzumab (or placebo) should be carefully handled during reconstitution. The indicated volume of pertuzumab (or placebo) solution should be withdrawn from the vials and added to a 250-cc IV bag of

0.9% Sodium Chloride Injection. Gently invert the bag to mix the solution. DO NOT SHAKE VIGOROUSLY. Visually inspect the solution for particulates and discoloration prior to administration. The entire volume within the bag should be administered as a continuous IV infusion. The volume contained in the administration tubing should be completely flushed using a 0.9% Sodium Chloride Injection.

The solution of pertuzumab (or placebo) for infusion diluted in polyvinyl chloride (PVC) or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted pertuzumab has been shown to be stable for up to 24 hours at room temperature (2°C–25°C). However, since diluted pertuzumab (or placebo) contains no preservative, the aseptically diluted solution should be stored refrigerated (2°C–8°C) for no more than 24 hours.

A rate–regulating device may be used for all study drug infusions.

Should extravasation of the study drug infusion occur, the following steps should be taken:

- Discontinue the infusion
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent
- If a significant volume of study drug remains, restart the infusion at a more proximal site in the same limb or on the opposite side

For further details, see the pertuzumab Investigator's Brochure.

4.3.1.2 Herceptin

Investigational Herceptin will be supplied by the Sponsor and will be labeled according to the regulatory requirements in China and the ICH guideline for Good Clinical Practice.

Herceptin will be provided as a freeze–dried preparation at a nominal content of 440 mg per vial. Herceptin is formulated in histidine, trehalose, and polysorbate 20. Once reconstituted, each solution contains 21 mg/mL of active drug at a pH of approximately 6.0.

Vials of Herceptin will be shipped at a temperature of 2°C–8°C (36°F–46°F), must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity, and should remain refrigerated until immediately prior to use. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. If a temperature deviation from the allowed 2°C–8°C is found either during shipment or storage, contact the Sponsor to determine whether the drug is still appropriate for use.

DO NOT FREEZE and DO NOT SHAKE the Herceptin vials. Store all vials within the outer carton, and protect them from light.

The medication must not be used beyond the expiration date stamped on the outer carton.

Each vial of Herceptin 440 mg is reconstituted with 20 mL of either Sterile Water for Injection (SWFI) or Bacteriostatic Water for Injection, USP, 1.1% benzyl alcohol preserved. If the Herceptin is reconstituted with SWFI, it is suitable for single use only.

Use of other reconstitution solvents is not allowed.

Appropriate aseptic techniques should be used. Herceptin should be carefully handled during reconstitution. Using a sterile syringe, slowly inject the SWFI in the vial containing the lyophilized Herceptin, directing the stream into the lyophilized cake. Swirl the vial gently to aid reconstitution. Herceptin may be sensitive to shear–induced stress (e.g., agitation or rapid expulsion from a syringe). DO NOT SHAKE. Vigorous handling of solutions of Herceptin results in aggregation of the protein and may create cloudy solutions. Causing excessive foaming during reconstitution or shaking the reconstituted Herceptin may result in problems with the amount of Herceptin that can be withdrawn from the vial.

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colorless to pale yellow transparent solution and should be essentially free of visible particulates.

The reconstituted solution contains 21 mg/mL of Herceptin, at a pH of approximately 6.0, and the appropriate calculated volume will be added in to 250 mL of 0.9% Sodium Chloride Injection.

Herceptin should not be mixed or diluted with other drugs. Do not administer as an IV push or bolus dose.

Determine the volume of the solution required on the basis of a loading dose of 8 mg of Herceptin per kilogram body weight, or a subsequent dose of 6 mg of Herceptin per kilogram body weight:

$$\textbf{Volume}\ (\text{in mL}) = \frac{\textbf{Body Weight}\ (\text{in kg}) \times \textbf{Dose}\ (8\ \text{mg/kg or } 6\ \text{mg/kg})}{\textbf{21 mg/mL}\ (\text{concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Do not use with glucose–containing solutions, since it causes aggregation of the protein. The bag should be gently inverted to mix the solution to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared, it should be administered immediately. If diluted

aseptically, it may be stored for a maximum of 24 hours from reconstitution (do not store above 30 C). No incompatibilities between Herceptin and PVC or polyethylene bags have been observed.

For further details, see the Herceptin local prescribing information and the Herceptin Investigator's Brochure.

4.3.1.3 Docetaxel

Docetaxel will be obtained locally by the investigational sites. Refer to the docetaxel prescribing information for information on formulation, preparation, and administration.

4.3.2 Dosage, Administration, and Compliance

Study treatment cycles are 3 weeks (21 ± 3 days) in length. The first dose of study treatment (Day 1 of Cycle 1) should be administered within 3 days after the date of randomization. Study treatments will be administered in the following sequence:

Pertuzumab (or Placebo) → Herceptin → Docetaxel

The treatment schedule, including details on dose, infusion duration, and observation period for each treatment, is summarized in Table 1.

Table 1 Study Treatment Schedule

Cycle	Blinded Pertuzumab (or Placebo)	Herceptin	Docetaxel
Cycle 1	Timepoint: Day 1	Timepoint: Day 1 Timing: After pertuzumab (or placebo) observation period	Timepoint: Day 1 Timing: After Herceptin observation period
	Dose: 840 mg Infusion duration: 60 min Observation period: 60 min	Dose: 8 mg/kg Infusion duration: 90 min Observation period: 60 min	Dose: 75 mg/m^2 Infusion duration: 60 min Observation period: According to institution standards
Subsequent cycles	Timepoint: Day 1	Timepoint: Day 1 Timing: After pertuzumab (or placebo) observation period	Timepoint: Day 1 Timing: After Herceptin observation period
	Dose: 420 mg [a] Infusion duration: 30 min or 60 min [b] Observation period: 30 min or 60 min [c]	Dose: 6 mg/kg [d] Infusion duration: 30 min or 90 min [e] Observation period: 30 min or 60 min [c]	Dose: 75 mg/m^2 Infusion duration: 60 min Observation period: According to institution standards

[a] If a patient misses a dose of pertuzumab (or placebo) (i.e., two sequential administration times are 6 weeks or more apart), a re-loading dose of 840 mg should be given. Subsequent doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

[b] If the first infusion of pertuzumab (or placebo) is tolerated without infusion–associated adverse events (fever and/or chills), the subsequent infusions may be delivered over 30 minutes.

[c] If the first infusion of pertuzumab (or placebo) or Herceptin is well tolerated without infusion–associated adverse events, the subsequent observational periods may be reduced from 60 minutes to 30 minutes.

[d] If a patient misses a dose of Herceptin (i.e., two sequential administration times are 6 weeks or more apart), a re-loading dose of 8 mg/kg should be given. Subsequent doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.

[e] If the first infusion of Herceptin is tolerated without infusion–associated adverse events (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

4.3.2.1 Pertuzumab (or Placebo) Dose and Schedule

Pertuzumab (or placebo) will be administered by IV infusion on Day 1 of each 3-week cycle, at a loading dose of 840 mg for Cycle 1 and a dose of 420 mg for subsequent cycles, until disease progression or unacceptable toxicity. The pertuzumab dose is not adjusted for any changes in body weight. No dose reduction will be allowed.

Administration may be delayed to assess or treat AEs such as cardiac AEs or myelosuppression. If a patient misses a dose of pertuzumab (or placebo) for one cycle (i.e., two sequential administration times are 6 weeks or more apart), a re-loading dose of 840 mg should be given. Subsequent doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

4.3.2.2 Herceptin Dose and Schedule

Herceptin will be administered by IV infusion on Day 1 of each 3-week cycle, at a loading dose of 8 mg/kg for Cycle 1 and a dose of 6 mg/kg for subsequent cycles, until disease progression or unacceptable toxicity. Baseline body weight will be used to calculate required doses of Herceptin. The dose of Herceptin will be re-calculated if a patient's body weight changes from baseline by ≥10%. If the dose is recalculated because of a ≥10% change in weight from baseline, this weight will then be used as the new baseline to calculate Herceptin dose in subsequent cycles. No dose reduction will be allowed, except in the case of body weight changes.

Administration may be delayed to assess or treat AEs such as cardiac AEs or myelosuppression. If a patient misses a dose of Herceptin for one cycle (i.e., two sequential administration times are 6 weeks or more apart), a reloading dose of 8 mg/kg should be given. Subsequent doses of 6 mg/kg will then be given every 3 weeks, starting 3 weeks later.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

4.3.2.3 Docetaxel

Docetaxel 75 mg/m^2 will be administered by IV infusion on Day 1 of each 3-week cycle. Prior to completion of Cycle 6, docetaxel should be discontinued only for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician.

Baseline body surface area will be used to calculate required doses of docetaxel. Weight and height should be recorded at baseline, and weight should be recorded at every scheduled visit. Height should be remeasured if the investigator thinks it is possible that the patient's height may have changed. Docetaxel dose adjustments due to changes in weight should be recalculated if the patient's weight has increased or decreased by ≥10% from baseline. If the dose is recalculated because of a ≥10% change in weight from baseline, this weight will then be used as the new baseline to calculate docetaxel dose in subsequent cycles. A nomogram will be provided for the determination of body surface area (see Appendix 5).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (pertuzumab, placebo, and Herceptin) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. Sites will obtain and utilize commercially available docetaxel.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Pertuzumab

The Sponsor will offer continued access to Roche IMPs (pertuzumab and Herceptin) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (pertuzumab and Herceptin) after completing the study if all of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive Roche IMPs (pertuzumab and Herceptin) after completing the study if any of the following conditions are met:

- *The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HER2-positive MBC*
- *The Sponsor has reasonable safety concerns regarding the IMP as treatment for HER2-positive MBC*
- *Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Patients may be eligible to receive pertuzumab as part of an extension study, as described in Section 3.1.1.

4.4 CONCOMITANT THERAPY AND PROCEDURES

4.4.1 Permitted Therapy and Procedures

All concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients should receive full supportive care (e.g., transfusion of blood and blood products, antibiotics) according to standard of care when necessary.

All protocol–allowed medications taken by the patient for concomitant disease should continue as necessary during the study and be recorded on the Concomitant Medications eCRF. The following list of permitted medications is provided as guidance. Treatments prescribed to patients should be adapted according to the local standard-of-care practices.

The following treatments and procedures are permitted:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines may be used according to local clinical practice for the prevention and treatment of infusion reactions associated with pertuzumab and/or Herceptin
- Medication to treat diarrhea (e.g., loperamide)
- Granulocyte colony-stimulating factor may be used according to the product license and according to the currently approved prescribing information for docetaxel and American Society of Clinical Oncology clinical guidelines (Smith et al. 2015)
- Steroids for docetaxel premedication and anti-emetics according to routine practice at each clinical site
- Inhaled steroids for asthma
- Bisphosphonates may be given according to their product license and routine clinical practice, at the investigator's discretion
- Palliative surgical procedures

  Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure, and any clinical findings.

- Placement of a central venous access device (CVAD)

  As a precautionary measure, it is recommended but not strictly required that CVAD placement be performed at least 7 days prior to initiation of study treatment. The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD–related thrombosis, infection, or dysfunction.

- Anticoagulation therapy for maintenance of patency of permanent indwelling IV catheters
- Palliative radiotherapy

  Radiotherapy is allowed only during the study treatment period for treatment of bone lesions present at baseline, if it is non-target lesion. If a patient requires radiation therapy to a new lesion, that new lesion would, per RECIST v 1.1, qualify as progressive disease.
- Acceptable non-hormonal methods of contraception (i.e., single or combined non-hormonal contraceptive methods that result in a failure rate of $<1\%$ per year)

4.4.2 Prohibited Therapy

The following treatments are not permitted:

- Treatment with other systemic anticancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or non–protocol-specified anticancer therapies
- Any oral, injected, or implanted hormonal methods of contraception
- Concurrent investigational agents of any type
- Initiation of herbal remedies for cancer treatment

  Herbal remedies initiated prior to study entry and continuing during the study are permitted and must be reported on the appropriate eCRF.

The following treatments should be avoided because of the risk of immunosuppression:

- Chronic or high-dose oral corticosteroid therapy
- TNF-α inhibitors
- Anti–T cell antibodies

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

An Eligibility Screening Form (ESF) documenting the patient's fulfillment of the entry criteria is to be completed by the investigator or a designee for all patients considered for the study and subsequently included or excluded. All ESFs should be kept in the study files at the sites. Additionally, copies of records of all prior Herceptin dosing in neoadjuvant or adjuvant setting and ECHO/MUGA reports should be retained with the study files at the investigative sites, for randomized and screen-failure patients.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases within the previous 5 years, breast cancer history (including tumor characteristics such as hormone-receptor status), prior cancer therapies and procedures (including any Herceptin treatment), complete cardiovascular history (including all prior LVEF values), smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 90 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Central Assessment of HER2 and ER/PgR Status and Biomarker Analyses

Mandatory tumor samples from the primary tumor (or metastatic sites, if the primary tumor is not available) will be submitted from all subjects during screening and submitted to a central pathology laboratory for assessment of HER2 via IHC and ISH for study eligibility, as well as for the assessment of ER/PgR status for patient stratification. Furthermore, tumor tissue biomarkers (e.g., PIK3CA mutation status and HER2/3 mRNA levels), will be determined to assess potential impact on prognosis of patients and/or pertuzumab/Herceptin response prediction. Markers, such as PD-L1 and CD8, may be assessed to explore association of immune markers to clinical outcome and benefit from HER2 targeted therapy.

Tumor tissue samples will be submitted in the form of either paraffin blocks or unstained, freshly cut slides containing formalin-fixed tumor tissue. Because uncontrolled oxidation processes on the slides may affect slides, tumor tissue blocks are preferred. However, if a tumor block is not available, 13 unstained freshly cut slides will be submitted, up to 15 slides as needed. From submitted tumor blocks, at the central laboratory, a maximum of 15 slides will be cut. The remaining part of the tumor block will be returned to the institution. HER2 and ER/PgR testing will be prioritized and the tissue will subsequently be used for assessment of biomarkers. A variety of technologies may be applied to assess the exploratory markers, which may include, but will not be limited to IHC, ISH, pCR-based methods, and sequencing technologies.

4.5.4 Physical Examinations

A complete physical examination should include measurements of height and weight and an evaluation of the head, and eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated jugular venous pressure [JVP], sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom–directed physical examinations, including weight measurement, should be performed. Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated JVP, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.5 Vital Signs

Vital signs will include measurement of heart rate and systolic and diastolic blood pressures while the patient is in a seated position and temperature. Vital signs will be recorded before and after infusion of each study medication (pertuzumab [or placebo], Herceptin, and docetaxel).

4.5.6 Tumor and Response Evaluations

Tumor assessments will be performed *as per local clinical practice and will continue until progressive disease or patient's death.* For patients who discontinue study treatment for reasons other than death, withdrawn consent, or investigator-determined progression events, efforts should be made to continue performing scheduled tumor assessments *as per local clinical practice* until patients' death or investigator-determined progressive disease. CT or MRI scans that were performed before a patient signed consent to take part in the study may be used to provide baseline tumor status as long as they were performed within 28 days prior to the start of treatment, at the same hospital, with the same technique or machine, and preferably by the same individual as those for tumor assessments during the study. This should be documented in the study files at the site.

RECIST v 1.1 (unidimensional tumor measurement) will be used to evaluate response and assess progressive disease. A summary of RECIST v 1.1 is provided in Appendix 4.

The minimum screening examinations should include the following:

- CT or MRI scan of the chest and abdomen (including liver, spleen, and adrenals)

  Positron emission tomography (PET) scans will not be considered for assessment of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).

  CT scans should be performed with a contrast agent. The CT portion of a combination PET/CT scan is generally not performed with contrast; therefore, PET/CTs are generally not acceptable. However, if the site has acquired a high-quality diagnostic CT scan including the application of contrast agent (which may be performed with modern PET/CT scanners), the CT scan portion may be adequate for submission and evaluation. For patients with known allergies to the contrast media, it is acceptable to perform a chest CT scan without contrast and an MRI scan for the abdomen (ideally at baseline and every tumor assessment thereafter).
- CT or MRI scan of the brain and/or spine if there is clinical suspicion of CNS metastases
- An isotope bone scan (with bone X-rays, as necessary) at baseline

  In the absence of radioactive isotopes, an MRI scan (with gadolinium enhancement, if required) or 18F-fluorodeoxyglucose PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases. Skeletal survey with plain X-rays is acceptable if there is no suitable alternative. The bone scan should be repeated in the event of clinical suspicion of progression of existing bone lesions or the appearance of new bone lesions.
- Medical photography to monitor chest wall recurrences (i.e., subcutaneous skin lesions)

The same assessment technique must be used throughout the study for evaluating a particular lesion (e.g., if a CT scan is used to assess metastatic lung lesions at baseline, a CT scan must be used at all subsequent tumor assessments to assess metastatic lung lesions). The same technique should also be used for cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid) and photographic data, if available. The same investigator should assess all tumor responses for each patient.

For patients with multiple measurable lesions, a maximum of 2 lesions per organ and 5 lesions in total that are representative of all involved organs should be designated as target lesions and recorded and measured at screening. All other lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the treatment period and follow-up, if applicable, until confirmed evidence of progressive disease. Tumor lesions that are situated within a field of previous irradiation can be considered measurable if these lesions have shown clinical evidence of

progression and can be reproducibly measured over time. Patients who have metastatic disease that is confined to the bone are not eligible for response evaluation but will be included in the PFS analysis if the criteria for progressive disease are satisfied (i.e., new bone lesions after treatment initiation).

Per RECIST v1.1, confirmatory measurements of complete and partial responses are not required. Stable disease must be confirmed at least 6 weeks after the RECIST v 1.1 criteria for stable disease have been met.

If there is suspicion of progression before the next scheduled tumor assessment, an unscheduled assessment is to be performed. The reason for the unscheduled assessment will be reported on the eCRF.

4.5.7 Cardiac Assessments

4.5.7.1 Electrocardiograms

Twelve-lead ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws.

4.5.8 Left Ventricular Ejection Fraction

All patients must have their LVEF assessed by 2D ECHO or MUGA scan as part of the screening process. The baseline LVEF assessment should be performed as close as possible to but a maximum of 42 days prior to, randomization. LVEF will be performed every 9 weeks from the date of randomization until the treatment discontinuation visit, or more frequently as needed for cardiac safety. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule of every 9 weeks from the date of randomization. After the treatment discontinuation visit, LVEF measurements will be performed every 6 months in the first year, then annually for up to 3 years until the end of the study. Patients for whom study treatment is permanently discontinued because of a decrease in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months, until the LVEF returns to ≥50% or until 1 year after the treatment discontinuation visit, whichever occurs first. Thereafter, LVEF assessments will be performed annually for up to 3 years until the end of the study after the treatment discontinuation visit.

ECHO is the preferred method because it can detect wall-motion abnormalities. LVEF is to be calculated using the modified Simpson method and must be ≥55% at baseline as determined by the local facility before a patient can be enrolled in the study. The investigator must decide which method of LVEF assessment (ECHO or MUGA scan) will

be used for each patient at baseline, and the same method and the same facility should be used throughout the study, to the extent possible. The LLN for the LVEF facility will be reported along with the LVEF result. Any prestudy LVEF values obtained during and after Herceptin neoadjuvant or adjuvant treatment will be obtained, as applicable.

4.5.9 Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells])

  Additional tests may be performed per the institution's standard practice.

- Serum chemistry

  Baseline and treatment discontinuation visit: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH

  Subsequent timepoints: potassium, creatinine, total bilirubin, ALP, ALT, AST

  Additional tests may be performed per the institution's standard practice.

- Coagulation (INR and aPTT or PT)

- Pregnancy test

  All women who are not postmenopausal (postmenopausal defined as $\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

The following samples will be sent to a central laboratory for analysis of HER2 and ER/PgR status:

- Tissue sample from the primary tumor for central determination of HER2 status by IHC and/or ISH and ER/PgR status by IHC

  A patient's HER2 status will be considered positive if the central laboratory confirms a score of 3+ by IHC in $>$ 10% of immunoreactive cells and/or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals $\geq$ 2.0) by ISH. The diagnosis should be made on the primary breast cancer specimen or on a biopsy of a metastatic site, if primary tumor is not available.

It is strongly recommended that an FFPE tissue block from the primary tumor (or metastatic site if the primary is not available) be submitted for central laboratory confirmation of HER2 eligibility. However, if that is not possible, unstained and freshly cut slides need to be submitted (See Section 4.5.3 for further details). The remaining part of the tumor block will be returned to the institution.

The patient's hormone receptor status will be determined by the central lab according to the American Society of Clinical Oncology-College of American Pathologists guidelines (Hammond et al. 2011). The ER and PgR status will be used as stratification factor but is not relevant to determine patient's eligibility. Tumors are considered hormone receptor positive if ER and/or PgR status is positive, tumors are considered negative if both ER and PgR are confirmed negative at central lab.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Tissue blocks submitted at baseline for eligibility screening and exploratory biomarker research will be returned in a batched manner every 6 months after the patient has been randomized into the trial. Slides will not be returned. Blocks can be returned immediately to sites upon request, in which case the number of slides needed for biomarker analyses will be freshly cut, and the block returned.

Stained slides will be kept as raw data for 15 years, and extracted material (DNA and RNA) will be stored for at least 5 years after clinical database closure.

4.5.10 Post-Study Follow-up

Patients who discontinue from the study for progressive disease or other reasons will receive treatment according to the local standard of care. After discontinuation of study treatment, information on survival and cancer-related therapies and medical or surgical procedures will be collected by telephone every 18 weeks until death until the end of the study, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

For further details on study drug modification and discontinuation, see Sections 5.1.1 and 5.1.2.

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Symptomatic left ventricular dysfunction (NCI CTCAE Grade 3 or 4) with a decrease in LVEF consistent with cardiac failure
- NCI CTCAE Grade 4 allergic reaction or acute respiratory distress syndrome

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The investigator will be notified if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Management of Risks Associated with Pertuzumab and Herceptin

Specific instructions for management of infusion hypersensitivity reactions (including anaphylaxis), symptomatic LVSD or asymptomatic decreases in LVEF, and HER1–related toxicities are provided below.

5.1.1.1 Infusion Hypersensitivity Reactions (Including Anaphylaxis)

Monoclonal antibodies may cause infusion–associated symptoms such as nausea, pyrexia, diarrhea, chills, fatigue, and headache. Such reactions typically occur during or shortly after an infusion.

In general (and in common with other antibody-associated infusion reactions), pertuzumab and Herceptin infusion–associated reactions are more frequent and severe with the first infusion, decrease in frequency and severity over time, and resolve fully. Infusion-associated reactions with pertuzumab are not affected by prior or concurrent Herceptin therapy; the incidence and severity of such reactions are similar regardless of prior or concurrent Herceptin.

Administration of pertuzumab and Herceptin should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored for any adverse effects during each infusion, for at least 60 minutes after the first pertuzumab (or placebo) infusion, and for at least 60 minutes after the first Herceptin infusion. The observation time for subsequent infusions can be decreased to 30 minutes if the infusions are well tolerated during Cycle 1.

Infusion of pertuzumab or Herceptin should be slowed or interrupted if the patient experiences infusion–associated symptoms (e.g., fever, chills, headache, fatigue, pruritus, nausea, vomiting, or diarrhea). Supportive care with oxygen, β-agonists, antihistamines, antipyretics, and corticosteroids may help alleviate symptoms. All infusion-associated symptoms must be resolved before Herceptin is given. Patients who experience infusion-related symptoms during or after infusions may be premedicated with analgesics and antihistamines for subsequent infusions. Patients who experience a Grade 4 allergic reaction or acute respiratory distress syndrome should be discontinued from treatment. Since there is the potential for a delayed onset of infusion-associated reactions, patients should be instructed to contact the treating physician with any concerns.

5.1.1.2 Symptomatic Left Ventricular Systolic Dysfunction and Asymptomatic Decrease in Left Ventricular Ejection Fraction

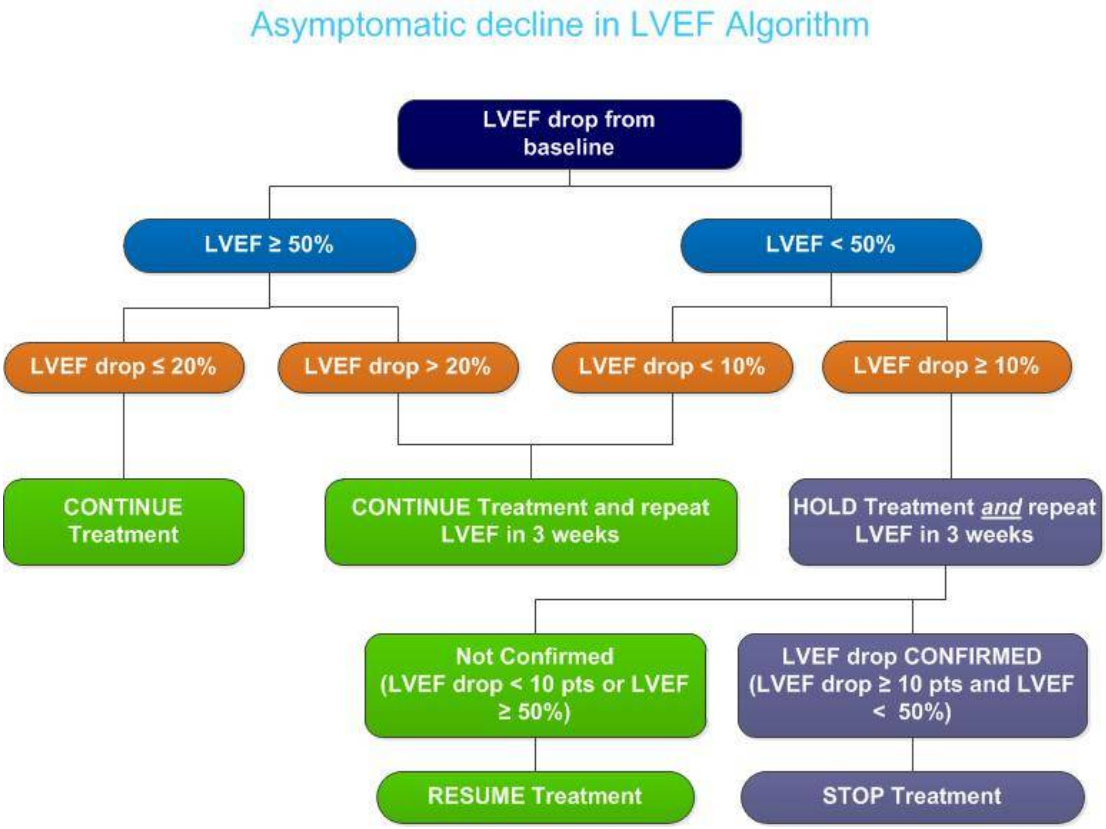
There is a risk of cardiac dysfunction with pertuzumab, as with Herceptin, because each of these antibodies is directed at the HER2 receptor. A decrease in LVEF has been observed in patients receiving pertuzumab; however, the majority of patients show improvement or return to baseline function on follow up (see Section 1.3.2.1).

All patients will undergo regular LVEF monitoring by ECHO or MUGA. Monitoring of LVEF is required while patients are receiving pertuzumab (or placebo) and Herceptin as well as after treatment completion as per the schedule of assessments (see Appendix 1).

If symptomatic LVSD symptoms develop, the patient must discontinue all study treatment. Symptomatic LVSD (heart failure) should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist, and the results of this evaluation should be reported on the eCRF.

Figure 2 summarizes the management of study treatment for patients who have an asymptomatic decrease in LVEF. The decision to continue or stop study treatment should be based on two factors: measured LVEF value and change in LVEF value from baseline.

Figure 2 Algorithm for Continuation or Discontinuation of Study Treatment Based on LVEF Assessments



LVEF = left ventricular ejection fraction.

Notes: Treatment is Herceptin and pertuzumab/placebo. LVEF drop should be evaluated using percentage points as unit.

Patients for whom study treatment was permanently discontinued because of a decrease in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months, until the LVEF returns to ≥50%, or 1 year after the treatment discontinuation visit, whichever occurs first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the treatment discontinuation visit.

5.1.1.3 Epidermal Growth Factor Receptor (HER1)-Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors. Diarrhea has been observed in approximately 60% of patients treated with pertuzumab in Phase II, single-agent studies (up to 90% of patients receiving pertuzumab in combination studies) and was Grade 1 or 2 in the majority of cases. For patients experiencing diarrhea, early intervention with loperamide should be recommended and patients should be treated with fluids and electrolyte replacement, as clinically indicated.

Rash has also been observed with EGFR tyrosine kinase inhibitors. The rash was generally mild to moderate in intensity and appeared to be treatable in some patients with standard acne therapies, including topical and oral antibiotics. To date, rash has been observed in approximately 17% of patients receiving pertuzumab in Phase II, single–agent studies (up to 40% of patients receiving pertuzumab in combination studies) and was generally Grade 1 or 2 in severity.

Mucositis has been observed in approximately 15% of patients receiving pertuzumab in Phase II single-agent studies and in up to 50% of patients in combination studies. The most common preferred terms reported were mucosal inflammation and stomatitis. Mucositis is generally not considered preventable, although for some cytotoxic agents, it may be reduced by cooling the mouth using ice chips before and during the infusion.

5.1.2 Dosage Modification and Treatment Interruption or Discontinuation

If any of the individual study drugs must be delayed for a day or more, all three agents should be delayed for the same timeframe.

Dosage modifications are not permitted for Herceptin (except in the case of body weight changes) or pertuzumab. Treatment interruption or discontinuation is permitted for toxicity, including cardiotoxicity (see Sections 4.6.2 and 5.1.1.2 for further information). Actions to be taken for toxicities related to Herceptin or pertuzumab are outlined in Table 2. The infusion should be slowed or interrupted if the patient experiences infusion-associated symptoms (e.g., fever, chills, headache, fatigue, pruritus, nausea, vomiting, and diarrhea; see Section 5.1.1.1). Supportive care with oxygen, β-agonists, antihistamines, antipyretics, and corticosteroids may help alleviate symptoms. All infusion-associated symptoms must be resolved before docetaxel is given or the patient is discharged. Patients who experience infusion-related symptoms during or after infusions may be premedicated with analgesics and antihistamines for subsequent infusions, with the first infusion administered over 60 (±10) minutes, followed by a 60-minute observation period. Patients who experience a Grade 4 allergic reaction or acute respiratory distress syndrome should be discontinued from treatment.

If pertuzumab/placebo or Herceptin is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment and will continue to be followed post-treatment, as described in Section 5.3.1.

Additionally, delays provided in Table 2 also apply to docetaxel.

Docetaxel may be delayed because of toxicity. If docetaxel is delayed for more than 3 weeks with no recovery, the patient should be withdrawn from docetaxel treatment. If docetaxel needs to be permanently discontinued, the patient will continue on pertuzumab (or placebo) and Herceptin.

Docetaxel dose reduction will be allowed for myelosuppression, hepatic dysfunction, and other toxicities (see Table 3).

Table 2 Actions to Be Taken for Toxicities Related to Herceptin or Pertuzumab

Toxicity	Action
Neutropenia	Hold all study treatment for up to 6 weeks. If recovery to ANC count ≥ 1000 cells/μL occurs within 6 weeks, resume all treatment. If recovery to ANC count ≥ 1000 cells/μL does not occur within 6 weeks, discontinue docetaxel.
Symptomatic LVSD	Discontinue all study treatment.
Asymptomatic decrease in LVEF	Follow instructions for holding, continuing, or discontinuing treatment as outlined above in Figure 2
Allergic reaction or acute respiratory distress syndrome: Grade 4	Discontinue all study treatment.
Other non-hematologic toxicities: [a] Grade 1 or 2	Continue all study treatment.
Other non-hematologic toxicities: [a] Grade 3 or 4	Hold all study treatment for up to 6 weeks. If recovery to Grade ≤ 2 occurs within 6 weeks, resume all treatment. If recovery to Grade ≤ 2 does not occur within 6 weeks, discontinue all study treatment.

ANC = absolute neutrophil count; NCI CTCAE = National Cancer Institute/ Common Terminology Criteria for Adverse Events; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction.

Notes: Severity grades for all events are based on NCI CTCAE v 4.0, with the exception of symptomatic LVSD, which should be graded according to NCI CTCAE v 4.0 for "heart failure" (Grade 2, 3, 4, or 5) and the New York Heart Association (NYHA) classification (see Appendix 5).

Study treatment refers to Herceptin, pertuzumab/placebo, and docetaxel.

a Includes non-hematologic toxicities not described above (e.g., cardiac toxicities other than symptomatic LVSD or asymptomatic decrease in LVEF).

Table 3 Docetaxel Dose Adjustments

Docetaxel Dose	Criteria
75 mg/m^2	Starting dose Administer only if neutrophil count is > 1500 cells/μL
55 mg/m^2	Reduce dose in case of any of the following toxicities: Febrile neutropenia or neutrophils < 500 cells/μL for more than 1 week (after fully recovering to a neutrophil count ≥ 1500 cells/μL) Platelets < 100,000 cells/μL (after recovering to a platelet count ≥ 100,000 cells/μL) Severe or cumulative cutaneous reactions

Docetaxel Dose	Criteria
Permanently discontinue docetaxel	After any of the following toxicities: Severe hypersensitivity reactions Grade > 3 peripheral neuropathy Severe or cumulative cutaneous reactions that continue at a dose of 55 mg/m^2 without recovery Febrile neutropenia or neutrophils < 500 cells/μL without recovery Platelets < 100,000 cells/μL without recovery Total bilirubin > ULN without recovery AST or ALT > 1.5 × ULN concurrent with serum ALP > 2.5 × ULN without recovery

ULN = upper limit of normal.

5.1.3 Pregnancy and Contraception

Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus) must agree to remain abstinent or use single or combined contraceptive methods that results in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment (based on PK).

Men participating in the study must agree to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose of study treatment.

Male study participants whose partners are pregnant should use condoms for the duration of the pregnancy.

Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

5.1.4 Breastfeeding

It is not known whether Herceptin or pertuzumab is excreted in human milk. Because maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or Herceptin therapy and not to breastfeed for at least 7 months following the last dose of either monoclonal antibody.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol–mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsy sample collection)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest (AESIs) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). AEs of special interest for this study include the following:

- A non-serious asymptomatic decrease in LVEF requiring treatment or leading to discontinuation of pertuzumab (or placebo) and Herceptin (must be reported in an expedited manner by using the SAE form and classifying the event as Non-Serious Event of Special Interest)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 through Section 5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsy sample collections, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported through the treatment discontinuation visit*, 28 days after the last dose of study drug. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.*

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE v 4.0 will be used for assessing severity of AEs. Table 4 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; or limiting age–appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life–threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life–threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

AEs that occur during or within 24 hours after study drug administration and judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" [IRR] or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion–Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion–Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For AEs other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient-evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every abnormal laboratory value qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as AEs.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated abnormal laboratory value should be classified as an AE.

If a clinically significant abnormal laboratory value is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant abnormal laboratory value is not a sign of a disease or syndrome, the abnormal value should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the abnormal laboratory value can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant abnormal laboratory value from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Vital Sign Values

Not every abnormal vital sign qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated abnormal vital sign should be classified as an AE.

If a clinically significant abnormal vital sign is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious AESI (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of breast cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

During survival follow-up, deaths attributed to progression of breast cancer should be recorded.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 5.2.2, except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  The patient has not suffered an AE
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Overdoses

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of pertuzumab or Herceptin are available.

5.3.5.13 Cardiac Adverse Events

All cardiac AEs occurring during the study and up to 12 months after last administration of study medications must be reported irrespective of causal relationship or seriousness. Grade $\geq$ 2 heart failure (symptomatic LVSD) must be reported for up to 3 years after last administration of study medications.

Symptomatic Left Ventricular Systolic Dysfunction (Heart Failure)

Symptomatic LVSD (heart failure) is a SAE that should be reported as a diagnosis, not as individual signs and symptoms thereof, on Adverse Events page. Specific related signs and symptoms will be entered on the eCRF. Symptomatic LVSD should be

graded according to NCI CTCAE v 4.0 (for "heart failure") and the NYHA classification (see Appendix 3).

Asymptomatic Left Ventricular Systolic Dysfunction

In general, asymptomatic decreases in LVEF should not be reported as AEs since LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decreases in LVEF of ≥ 10 percentage points from baseline to an LVEF of < 50% must be reported as an AE.
- An asymptomatic decreases in LVEF requiring treatment or leading to discontinuation of pertuzumab (or placebo) and Herceptin must be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions) as a non-serious AESI.

Asymptomatic decreases in LVEF should be reported as "ejection fraction decreased" and graded according to NCI CTCAE v 4.0. Table 5 summarizes the reporting conventions for LVSD.

Table 5 Reporting Conventions for Left Ventricular Systolic Dysfunction

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decrease in LVEF of ≥ 10 percentage points from baseline to an LVEF < 50%	Adverse event (eCRF)	"Ejection fraction decreased"	NCI CTCAE for " ejection fraction decreased "
Asymptomatic decrease in LVEF requiring treatment or leading to discontinuation of pertuzumab (or placebo) and Herceptin	Non-serious adverse event of special interest (eCRF), with expedited reporting (see Section 5.4.2)	"Ejection fraction decreased"	NCI CTCAE for " ejection fraction decreased "
Symptomatic left ventricular systolic dysfunction (congestive heart failure)	Serious adverse event (eCRF) and Symptomatic Left Ventricular Systolic Dysfunction eCRF, with expedited reporting (see Section 5.4.2)	"Heart failure"	NCI CTCAE for " heart failure" and NYHA classification
Asymptomatic decrease in LVEF of < 10 percentage points from baseline or to an LVEF ≥ 50%	No adverse event reporting required; LVEF values to be reported on eCRF	NA	NA

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; LVEF = left ventricular ejection fraction; NA = not applicable; NYHA = New York Heart Association.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and Institutional Review Board/Independent Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor (F. Hoffmann-La Roche Medical Responsible) Contact Information

Primary Contact
Medical Monitor: [redacted], *M.D.*
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

Secondary Contact
Medical Monitor: [redacted], M.D.
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the F. Hoffmann-La Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events Occurring prior to Initiation of Study Drug

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol–mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2.2 Events Occurring after Initiation of Study Drug

After initiation of study drug, SAEs and non-serious AEs of special interest will be reported through the treatment discontinuation visit. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting *serious adverse events that occur >28 days after the final dose of study treatment* are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to

Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion should be classified as a SAE (because the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial–related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study or within 7 months after the last dose of study medication should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For SAEs, non-serious AESI, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Additional information on any pertuzumab-exposed pregnancy (and an infant resulting from that pregnancy) will be requested by Roche Drug Safety at specific time points (i.e., at the end of the second trimester, 2 weeks after expected date of delivery, and at 3, 6, and 12 months of the infant's life).

5.6 ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

After the end of the AE reporting period (*as defined in Section 5.3.1*), *all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.*

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use

of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to *the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.*

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Pertuzumab Investigator's Brochure
- Local prescribing information for Herceptin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to assess whether the addition of pertuzumab to the combination of Herceptin and docetaxel prolongs PFS in Chinese patients in a manner consistent with the results from CLEOPATRA. A consistency threshold is defined as a hazard ratio of < 0.81, which maintains $\geq 50\%$ of the risk reduction determined in CLEOPATRA (hazard ratio, 0.62).

To reliably determine the predefined consistency value, a simulation method was used to estimate the required sample size. A total of 240 patients randomized in a 1:1 ratio and 123 PFS events in the two treatment arms are required, providing an appropriate 83% probability of showing consistency.

The sample size estimation was based on the following assumptions:

- The median PFS is 11 months in the control arm, with a PFS hazard ratio of 0.68
- The recruitment period is estimated to be 15 months

The primary analysis of PFS will be performed after 123 PFS events have occurred, and the required PFS events are expected to be reached at around 23 months.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, duration of follow-up, and discontinuation from the study and reasons for discontinuation will be summarized by treatment arm for all randomized patients. In addition, major protocol violations will be summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographics and baseline characteristics, such as age, weight, ECOG Performance Status, ER/PgR status, HER2 status (IHC test score of 3+ and/or ISH amplification ratio of $\geq$ 2.0), prior treatments for breast cancer, treatment–free survival, and involvement of visceral sites, will be summarized by treatment arm.

Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, following the intent-to-treat principle, with patients grouped according to the treatment assigned at randomization. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only patients with an objective response will be included in the analysis.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on investigator assessments. PFS is defined as the time from randomization to the first occurrence of progressive disease, as determined by the investigator using RECIST v 1.1, or death from any cause within 18 weeks after the final tumor assessment, whichever occurs first.

At the time of data cutoff for the PFS analysis, data for patients who do not have documented progressive disease or who have not died within 18 weeks of the last tumor assessment will be censored at the time of the last tumor assessment (or, if no tumor assessments are performed after the baseline visit, at the time of randomization plus 1 day).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazards model, stratified by disease type (visceral disease vs. non-visceral disease) and hormone receptor status (ER and PgR negative or ER and/or PgR positive), will be used to estimate the hazard ratio between the two treatment arms and its 95% CI. The unstratified hazard ratio will also be provided. The two-sided stratified log–rank test will be used to compare PFS between the two treatment arms. The unstratified log-rank test result will also be provided.

Sensitivity analyses are planned for PFS to account for the potential bias introduced by missed visits, timing of death, and non–protocol-specified anticancer therapy. Details will be described in the Statistical Analysis Plan.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study include OS, objective response rate, and duration of objective response.

6.4.3 Exploratory Analyses

Biomarker analyses will be of exploratory nature only and all analyses will be of descriptive nature.

6.4.3.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the date they were last known to be alive. Patients with no post-baseline information will be censored at the time of randomization plus 1 day. Analysis methods are the same as those described for the primary endpoint.

OS data will be summarized at the time of final PFS analysis, at approximately 23 months. A final analysis of OS will be performed at approximately 3 years after randomization of the last patient.

The 1-year survival rate will also be estimated using the Kaplan-Meier method. A 2-year landmark analysis will be performed, in the form of a truncated survival analysis at 2 years. A truncated survival endpoint at 2 years is considered a robust and clinically highly relevant endpoint for capturing clinical benefit of a new therapy. In this analysis, only those deaths occurring within 2 years of randomization will be counted as events.

6.4.3.2 Objective Response Rate

ORR is defined as a CR or PR that is confirmed 28–42 days later, as determined by the investigator using RECIST v 1.1. Only patients with measurable disease at baseline will be included in the analysis of ORR. Patients without a post-baseline tumor assessment will be considered non-responders.

An estimate of the ORR and its 95% CI (Pearson-Clopper) will be calculated for each treatment arm. The difference in ORR will also be provided with 95% CIs (using Hauck-Anderson method). The Mantel-Haenszel $\chi 2$ test, stratified by disease type (visceral disease vs. non-visceral disease) and hormone receptor status (ER and PgR negative or ER and/or PgR positive) will be used to compare the ORR between the two treatment arms. An unadjusted Fisher's exact test result will also be provided.

6.4.3.3 Duration of Response

Duration of response is defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v 1.1, or death from any cause, whichever occurs first. Only patients with an objective response will be included in the analysis. The method for handling censoring is the same as that described for the primary endpoint.

Median duration of objective response for each treatment arm will be estimated using the Kaplan-Meier approach. The hazard ratio between the two treatment arms will also be estimated using Cox regression.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety analysis population, which will consist of all patients who receive at least one dose of any of the study drugs, with patients grouped according to the treatment actually received.

6.5.1 Study Drug Exposure

The numbers of patients who experience any dose interruption (including dose delays), dose modification, or dose discontinuation will be summarized by treatment arm. Descriptive statistics will be presented for total cumulative dose, number of cycles, and patient frequency of treatment cycles.

6.5.2 Adverse Events

Verbatim descriptions of treatment–emergent adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v 4.0. All AEs, including SAEs, will be summarized by treatment arm and NCI CTCAE grade. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AE, the maximum severity recorded will be used in the summaries.

Deaths reported during the study treatment period and those reported after patient treatment discontinuation will be summarized by treatment group.

6.5.3 Cardiac Safety

The number and percentage of patients with symptomatic LVSD at any time during the study will be summarized by treatment arm. In addition, the number and percentage of patients with significant asymptomatic decrease in LVEF (defined as an absolute decrease of $\geq$ 10 percentage points from baseline to an LVEF of $<$ 50%) at any time during the study will be summarized by treatment arm.

LVEF measurements and change in LVEF from baseline will be summarized by treatment arm.

6.5.4 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Changes in laboratory data will be summarized by grade using NCI CTCAE v 4.0 for each treatment arm. Selected abnormal laboratory values, such as worst toxicity grade and toxicity grade shift from baseline, will be summarized by treatment arm.

6.6 EXPLORATORY ANALYSES

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint, PFS, across important subgroups, forest plots (including estimated hazard ratios) will be provided for the following variables: age, disease type (visceral disease vs. non-visceral disease), ECOG Performance Status, adjuvant/neoadjuvant therapy, treatment–free interval ($<$ 2 years versus $>$ 2 years vs. no prior therapy), hormone receptor status (ER and/or PgR positive versus ER and PgR negative), HER2 status by central testing.

If applicable, expanded analyses will be performed using Cox regression models to estimate treatment effect by adjusting covariates in an exploratory manner. Variables to be considered are the stratification factors as well as other disease– or patient–related prognostic or predictive factors.

6.7 INTERIM ANALYSES

There are no interim analyses planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Local laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Radiographic tumor assessment films (including but not limited to chest X-rays, CT scans, MRI scans, and bone scans), and ECHO/MUGA cardiac assessments will not be reported through the EDC system.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor–designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial–related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written Investigational New Drug (IND) safety reports or other safety–related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. Food and Drug Administration and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., 3 years after the last patient is enrolled or progressive disease is identified in all patients, whichever is earlier).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL VIOLATIONS

The investigator should document and explain any protocol violations. The investigator should promptly report any violations that might impact patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Roche. An IxRS will be utilized to collect patient screening information and to randomize eligible patients to one of the two treatment arms. Up to approximately 20 sites in China will participate in this study, enrolling approximately 240 patients. Roche will provide clinical operations oversight, data management support, and medical monitoring.

Tumor tissue samples will be sent to a central laboratory for analysis. Sample analysis will be performed by an external vendor or Roche.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC. Approval must be obtained from the IRB/EC before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Agus DB, Gordon MS, Taylor C, et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. J Clin Oncol 2005;23:2534–43.

Baselga J, Cameron D, Miles D, et al. Objective response rate in a phase II multicenter trial of pertuzumab (P), a HER2 dimerization inhibiting monoclonal antibody, in combination with trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC) which has progressed during treatment with T. J Clin Oncol 2007 ASCO Annual Meeting Proceedings;25:18S (Suppl June 20):1004.

Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. Clin Breast Cancer 2010;10:489–91.

Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19

Bernard-Marty C, Cardoso F, Piccart M. Facts and controversies in systemic treatment of breast cancer. Oncologist 2003;9:617–32.

Bieche I, Onody P, Tozlu S, et al. Prognostic value of ERBB family mRNA expression in breast carcinomas. Int J Cancer 2003;106:758–65.

Bilous M, Morey AL, Armes JE, et al. Assessing HER2 amplification in breast cancer: findings from the Australian In Situ Hybridization Program. Breast Cancer Res Treat 2012;134:617–24.

Chia S, Norris B, Speers C, et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol. 2008; 26(35):5697–704

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;421:756–60.

Chung C, Carlson R. Goals and objectives in the management of metastatic breast cancer. Oncologist 2003;8:514–20

Cobleigh MA, Vogel CL, Tripathy D, et al. Efficacy and safety of Herceptin® (humanized anti-HER2 antibody) as a single agent in 222 women with HER2 overexpression who relapsed following chemotherapy for metastatic breast cancer. J Clin Oncol 1998;17:376A.

Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [resource on the Internet]. 2010 [Updated 2010; cited October 2013]. Available from: http://globocan.iarc.fr.

Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell 2004;5(4):317–28.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733–43.

Guy PM, Platko JV, Cantley LC, et al. Insect cell-expressed P180(Erbb3) possesses an impaired tyrosine kinase-activity. Proc Natl Acad Sci USA 1994;91:8132–6.

Hammond ME. ASCO-CAP guidelines for breast predictive factor testing: an update. Appl Immunohistochem Mol Morphol. 2011;19:499–500.

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.

Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol 2006;24:4963–70.

Herceptin® (Trastuzumab) U.S. Package Insert, Genentech.

National Cancer Center, Disease Prevention, Control Bureau, and Ministry of Health, Eds., 2012 Chinese Cancer Registry Annual Report, Military Medical Science Press, Beijing, China, 2012.

Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.

Jones RB, Gordus A, Krall JA, et al. A quantitative protein interaction network for the ErdB receptors using protein microarrays. Nature 2006;439:168–74.

Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2 positive metastatic breast cancer administered at first line treatment (The M77001 Study group). J Clin Oncol 2005;23:4265–74.

Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006 23;1275–84

Pathmanathan N, Provan PJ, Mahajan H, et al. Characteristics of HER2-positive breast cancer diagnosed following the introduction of universal HER2 testing. Breast 2012;21:724–9.

Pauletti G, Dandekar S, Rong H, et al. Assessment of methods for tissue-based detection of the HER-2neu alteration in human breast cancer: a direct comparison of fluorescent in-situ hybridization and immunohistochemistry. J Clin Oncol 2000;18:3651–64.

Pawlowski V, Revillion F, Hornez L, et al. A real-time one-step reverse transcriptase-polymerase chain reaction method to quantify c-erbB-2 expression in human breast cancer. Cancer Detect Prev 2000;24(3):212–23.

Portera CC, Walshe JM, Rosing DR, et al. Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. Clin Cancer Res 2008;14:2710–6.

Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–84.

Ross JS, Slodkowska EA, Symmans WF,et al. The HER-2 Receptor and Breast Cancer: Ten Years of Targeted Anti-HER-2 Therapy and Personalized Medicine. Oncologist 2009;14:320–368.

Slamon DJ, Clark GM, Wong SG, et al. Huam breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER-2 for metastatic breast cancer. N Engl J Med 2001;344;783–92.

Sliwkowski MX. Ready to partner. Nature Struct Biol 2003;10(3):158–9.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Onc 2015;33:3199-3212.

Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. Curr Oncol Rep 1999;1:16–22.

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.

Swain SM, Baselga José, Kim Sung-Bae, et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer (CLEOPATRA study). N Engl J Med 2015;372:724-734.

Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23(31):7811–19.

Therasse P, Arbuck SG, Eisenhauer EA, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst 2000;92(3):205–16.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Planning Inference 2001;99:25–40.

Witton CJ, Reeves JR, Going JJ, et al. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. J Pathol 2003;200(3):290–7.

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nature Rev Mol Cell Biol 2001;2:127–37.

Xiao hong H, Yuan-kai S, Li M, et al. A prospective multicenter study of HER-2/neu status in human breast cancer patients of mainland China: comparison of fluorescence in situ hybridization and immunohistochemistry. China J Lab Med 2010;33(7):655.

Appendix 1
Schedule of Assessments

	Screening [a,b]		Treatment Period [a]		Follow-Up [a]			
			Every Cycle (21 days)		Treat. Discon. Visit	Week 18 after Treat. Discon. Visit	Every 18 Weeks after Treat. Discon. Visit	
Day	–28 to –1	–7 to –1	1	Every 3 Cycles	28–42 Days after Final Treatment [c]	126 Days after Treat. Discon. Visit	Every 126 Days after Treat. Discon. Visit	Up to 3 Years after Treat. Discon. Visit
Informed consent	x [d]							
Archival tumor tissue for HER2 eligibility, ER/PgR status, and exploratory BM analyses to central laboratory	x [d]							
Complete medical history	x							
Review of eligibility criteria	x							
Complete physical examination [e] and vital signs [f]	x							
Symptom-directed physical examination [g] and vital signs [f]			x		x			
LVEF by ECHO or MUGA	x [h]		Every 9 weeks from randomization [i]		x	Every 6 months in the first year, then annually for up to 3 years [j]		
12-Lead ECG	x		Every 9 weeks, at same time as LVEF [i]		x			
Chest X-ray	x		If indicated		x [k]	If indicated		
ECOG Performance Status	x		x		x			
Tumor assessments	x [l,m]		*As per clinical practice* [l,n]					

Appendix 1
Schedule of Assessments (cont.)

	Screening [a,b]		Treatment Period [a]		Follow-Up [a]			
			Every Cycle (21 days)		Treat. Discon. Visit	Week 18 after Treat. Discon. Visit	Every 18 Weeks after Treat. Discon. Visit	
Day	–28 to –1	–7 to –1	1	Every 3 Cycles	28–42 Days after Final Treatment [c]	126 Days after Treat. Discon. Visit	Every 126 Days after Treat. Discon. Visit	Up to 3 Years after Treat. Discon. Visit
Bone scan	x		If indicated [o]					
Brain scan	x [p]		Every 9 weeks from randomization [q]					
Adverse events	x [r]		Ongoing [s]					
Concomitant medications and cancer-related surgery/procedures	x [t]		Ongoing		Ongoing			
Pertuzumab/placebo administration			x [u,v]					
Herceptin administration			x [u,w]					
Docetaxel administration			x [u,x]					
Hematology, at local laboratory		x [y,z]	x [y,z]		x [z]			
Chemistry, at local laboratory		x [y,aa]	x [y,bb]		x [aa]			
INR and aPTT or PTT, at local laboratory		x	x [cc]		x			
Pregnancy test, at local laboratory		x [dd]		x [dd]	x [dd]	3 and 7 months after treatment discontinuation visit [dd]		
Cancer-related procedures and therapies							x [ee]	
Survival information							x [ee]	

Appendix 1
Schedule of Assessments (cont.)

aPTT = activated partial thromboplastin time; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition; PET = positron emission tomography; PgR = progesterone receptor; PTT = partial thromboplastin time; Treat. Discon. = Treatment Discontinuation.

[a] Unless otherwise noted, a window of ±3 days will apply to all visits and assessments, except for collection of follow-up survival information, which will have a window of ±7 days. *Study assessments/cycles may be adjusted slightly to accommodate holidays, vacations, and unforeseen major life events. Documentation justifying this decision should be provided.*

[b] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and *within 28 days prior to first study treatment may be used; such tests do not need to be repeated for screening, with the exception of INR, aPTT/ PTT, chemistry, hematology, and pregnancy evaluations performed prior to obtaining informed consent and >7 days prior to Day 1 of Cycle 1.*

[c] The treatment discontinuation visit should occur 28–42 days after the last administration of study treatment (pertuzumab (or placebo), Herceptin, or docetaxel), whichever is discontinued last.

[d] Signing of the Informed Consent Form and submission of tumor sample for HER2 eligibility are not limited to the 28-day window prior to Day 1 of Cycle 1.

[e] Includes measurements of height and weight and an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation).

[f] Vital signs (blood pressure, pulse rate, and body temperature) will be recorded before and after infusion of each study medication (pertuzumab (or placebo), Herceptin, and docetaxel).

[g] Perform a limited, symptom-directed examination, including weight measurement, at specified timepoints or as clinically indicated. Particular care should be taken with regard to cardiovascular signs and symptoms. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[h] Perform as close as possible to, but a maximum of 42 days prior to, randomization. Any prestudy LVEF values obtained during and after Herceptin neoadjuvant or adjuvant treatment will be obtained, as applicable.

[i] Perform every 9 weeks from the date of randomization until the treatment discontinuation visit, or more frequently as needed for cardiac safety. If an LVEF assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule of every 9 weeks from the date of randomization. Perform a 12-lead ECG at the same time as the LVEF assessment.

[j] Patients for whom study treatment is permanently discontinued because of a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months, until the LVEF returns to ≥50%, or 1 year after the treatment discontinuation visit, whichever occurs first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the treatment discontinuation visit.

[k] If not performed within 28 days prior to the treatment discontinuation visit.

[l] The same assessment technique must be used throughout the study for evaluating a particular lesion. The same technique should also be used for cytologic (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid) and photographic data, if available. The same investigator should assess all tumor responses for each patient.

[m] MRI or CT scans that were performed before a patient signed consent to take part in the study may be used to provide baseline tumor status as long as they were performed within 28 days prior to the start of treatment, at the same hospital, with the same technique or machine, and preferably by the same individual as those for tumor assessments during the study. This should be documented in the study files at the site.

[n] Tumor assessments will be performed *as per local clinical practice and will continue until progressive disease or patient's death*. All patients should undergo, at a minimum, a chest and abdomen CT or MRI scan. PET scans will not be considered for assessment of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).

[o] A bone scan should be performed in the event of clinical suspicion of progression of existing bone lesions or the appearance of new bone lesions. If treatment is discontinued because of disease progression at sites other than bone, a bone scan should be performed immediately. In the absence of radioactive isotopes, an MRI scan (with gadolinium enhancement, if required) or ^{18}F-fluorodeoxyglucose PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases. Skeletal survey with plain X-rays is acceptable if there is no suitable alternative.

[p] CT or MRI scan of the brain and/ or spine within 28 days before randomization in cases of clinical suspicion of brain metastases.

[q] CT or MRI scan of the brain and/or spine if there is clinical suspicion of CNS metastases.

[r] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

[s] After initiation of study drug, all adverse events will be reported through the treatment discontinuation visit. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any poststudy serious adverse events or non-serious adverse events of special interest (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[t] Includes all medications taken within 90 days prior to randomization.

[u] Patients will receive study treatment (pertuzumab (or placebo) followed by Herceptin and then docetaxel) by IV infusion on Day 1 of each 3-week cycle. The first dose of study treatment (Day 1 of Cycle 1) must be administered within 3 days of randomization. Treatment with pertuzumab (or placebo) and Herceptin will continue until disease progression or unacceptable toxicity. Prior to completion of Cycle 6, docetaxel should only be discontinued for disease progression or unacceptable toxicity. After completion of Cycle 6, discontinuation of docetaxel treatment is at the discretion of the patient and treating physician. See Section 4.3 for additional details.

[v] Patients will receive either placebo or pertuzumab at a loading dose of 840 mg for Cycle 1, followed by 420 mg for subsequent cycles.

[w] Patients will receive Herceptin at a loading dose of 8 mg/kg for Cycle 1, followed by 6 mg/kg for subsequent cycles.

[x] Patients will receive docetaxel at a dose of 75 mg/m^2.

[y] Laboratory tests must be performed within 3 days prior to each study drug administration, and results must be available prior to each study drug infusion. In general, if baseline laboratory assessments are performed within 7 days prior to study treatment start, they will not need to be repeated on Day 1 of the start of study treatment.

[z] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[aa] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH.

[bb] Includes potassium, creatinine, total bilirubin, ALP, ALT, AST.

[cc] During the treatment period, patients receiving therapeutic doses of anti-coagulants should have INR and aPTT or PTT measurements repeated before the start of every chemotherapy cycle. Results must be available prior to each study drug infusion.

[dd] All women who are not postmenopausal (postmenopausal defined as $\geq$12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. A urine pregnancy test will be performed at all other specified timepoints (and as clinically indicated). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Baseline and treatment period pregnancy test results must be available prior to drug infusion.

[ee] After discontinuation of study treatment, information on survival and cancer-related therapies and medical or surgical procedures will be collected by telephone every 18 weeks until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. Immediately prior to the data cutoff for the primary progression-free survival analysis and for any overall survival analysis, the investigative sites will contact every patient that is alive to confirm current survival status.

Appendix 2
ECOG Performance Status Scale

Grade	Scale
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, i.e., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Appendix 3
NYHA Classification and NCI CTCAE v. 4.0 Grading for Left Ventricular Systolic Dysfunction

NYHA Classification for Symptomatic Left Ventricular Systolic Dysfunction (Heart Failure)

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997

NCI CTCAE Version 4.0 Grading for Heart Failure and Ejection Fraction Decreased

Heart Failure (Symptomatic Left Ventricular Systolic Dysfunction)

Grade1	Asymptomatic with laboratory or cardiac imaging abnormalities
Grade 2	Symptoms with mild to moderate activity or exertion
Grade 3	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Please refer to the NCI CTCAE v 4.0 for further details.

Appendix 3
NYHA Classification and NCI CTCAE v. 4.0 Grading for Left Ventricular Systolic Dysfunction (cont.)

Ejection Fraction Decreased (Asymptomatic Left Ventricular Systolic Dysfunction)

Grade1	-
Grade 2	Resting ejection fraction (EF) 50 - 40%; 10 -19% decrease from baseline
Grade 3	Resting ejection fraction (EF) 39 - 20%; >20% decrease from baseline
Grade 4	Resting ejection fraction (EF) <20%
Grade 5	-
Please refer to the NCI CTCAE v 4.0 for further details.	

- N/A

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

Measurable Tumor Lesions

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

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

---

[1] 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.
[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

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

Blastic bone lesions are non-measurable.

Cystic Lesions:

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

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

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality

and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally

reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

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

Complete response (CR): Disappearance of all target lesions

Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.

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

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The appearance of one or more new lesions is also considered progression.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

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

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is

seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s)

would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to

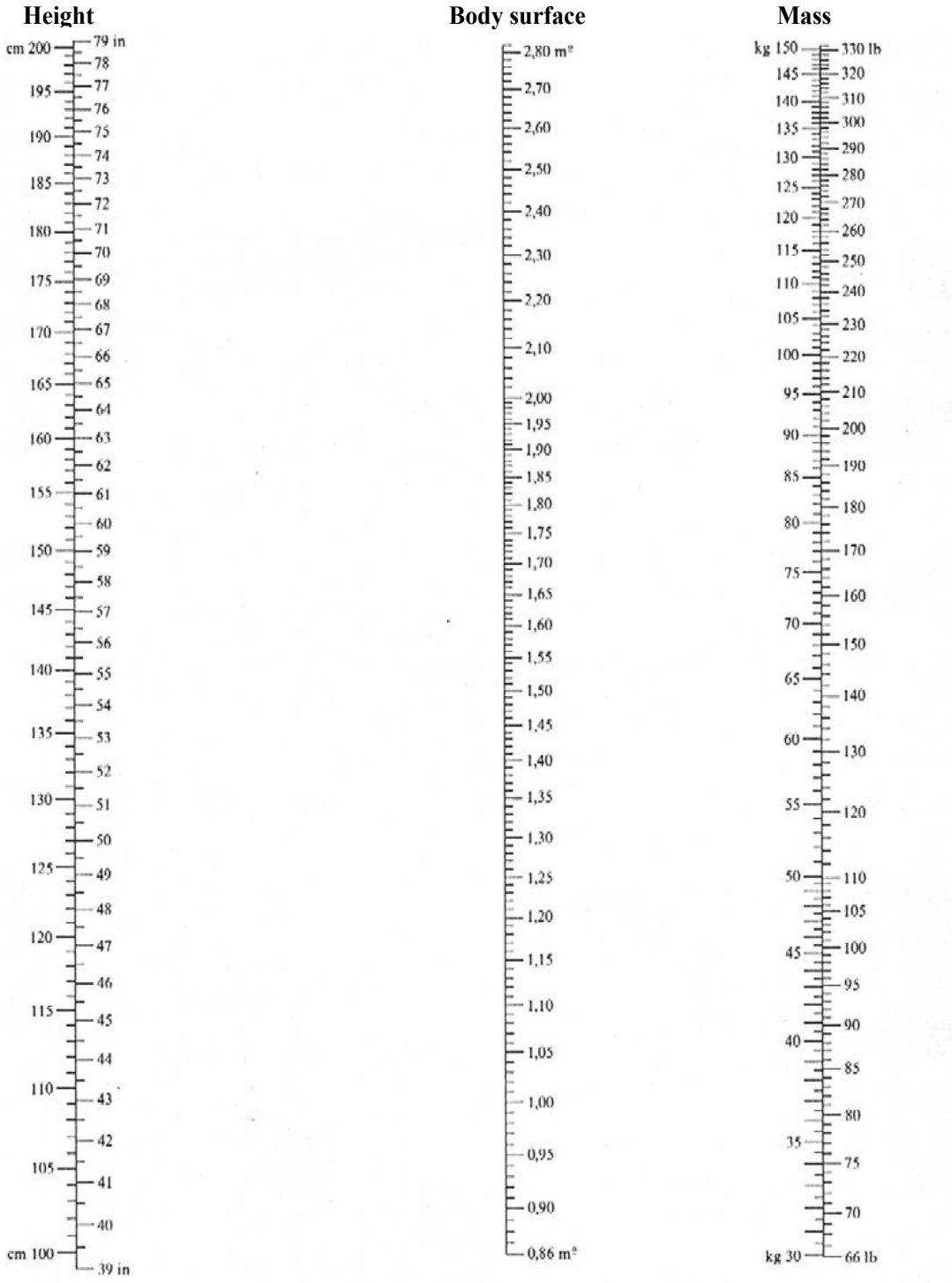
overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
Nomogram for the Determination of Body Surface Area



Based on the Formula from Du Bois and Du Bois, Arch.intern.Med., 17, 863 (1916): $0 = M^{0,425} \times L^{0,725} + x71,84$ resp. $\log 0 = \log M \times 0,425 + \log L \times 0,725 + 1,8564$
(0: Body surface [in cm2], M; Body mass [in kg]: L: Body length [in cm]