Official Title: **A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDY TO EVALUATE PERTUZUMAB IN COMBINATION WITH DOCETAXEL AND TRASTUZUMAB AS NEOADJUVANT THERAPY, AND PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AS ADJUVANT THERAPY AFTER SURGERY AND CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE OR LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER**

NCT Number: **NCT02586025**

Document Date: **PROTOCOL**

Version 4: 06 December 2016

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDY TO EVALUATE PERTUZUMAB IN COMBINATION WITH DOCETAXEL AND TRASTUZUMAB AS NEOADJUVANT THERAPY, AND PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AS ADJUVANT THERAPY AFTER SURGERY AND CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE OR LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	YO28762
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 5 March 2013
DATES AMENDED:	Version 2: 4 August 2014 Version 3: 15 August 2014 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	06-Dec-2016 18:25:11

CONFIDENTIAL

This clinical study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland. However, it may be implemented in individual countries by Roche's local affiliates, including Genentech, Inc. in the United States. The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Roche except to the extent necessary to obtain informed consent from persons to whom the drug may be administered.

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol YO28762 has been amended to change the timing of the primary efficacy analysis. The primary efficacy objective of the study is to evaluate the total pathologic complete response (tpCR) rate as assessed by an Independent Review Committee. The timing for the primary efficacy analysis has been changed to occur when all patients who are eligible for surgery have completed surgical treatment with the assessment of pathological response (i.e., after surgical treatment following neoadjuvant therapy). The previous timing specified that the analysis would occur when all patients had completed the treatment completion or discontinuation visit (i.e., after completion of all neoadjuvant and adjuvant study treatments). To conduct the primary analysis after surgery when all patients can be assessed for the primary efficacy endpoint is consistent with globally-accepted scientific conduct of neoadjuvant studies. The timing of the primary analysis after surgery is also consistent with other pertuzumab neoadjuvant studies that have been accepted as the basis for regulatory approvals in the United States and the European Union (Section 6.4.1).

Additional changes to the protocol are as follows:

- The clinical experience of patients with early-stage breast cancer who were treated with pertuzumab in Studies WO20697 (NeoSphere) and BO22280 (TRYPHAENA) studies has been updated (Section 1.2.2).
- The eligibility requirement that the baseline tumor must be >2 cm in the longest diameter includes all enrolled patients and has been clarified in Sections 3.1.1 and 4.5.1.4, respectively.
- The planned Safety Monitoring Committee has been replaced by the Sponsor's study team, which will review adverse events, serious adverse events, and any other safety data in the study on a regular and ongoing basis. The study team will be responsible to review accumulating safety data, assess and monitor ongoing safety in patients, evaluate potential changes to the clinical study protocol, and ultimately safeguard patient safety (Sections 1.4 and 3.1.3). Overall data to date indicate that pertuzumab is well tolerated as a monotherapy and that it can be administered in combination with trastuzumab and other therapeutic agents with manageable additional toxicity.

  As of 7 December 2015, an estimated 10,215 patients (which includes Asian and Chinese patients) had received pertuzumab in Roche-sponsored studies in which pertuzumab is an investigational medicinal product. No unexpected toxicities were encountered other than those that are known for agents that target human epidermal growth factor (HER) receptors.
- The exploratory objectives for biomarkers have been updated to include programmed death–ligand 1 (PD-L1) and other biomarkers that are relevant to breast cancer (Section 2.3). The rationale for biomarker and laboratory assessments has been revised accordingly (Sections 3.3.6 and 4.5.1.5).

- The number of participating sites has been updated from 28 sites to approximately 24 sites (Section 3.1.1).
- The types of hormonal therapy for premenopausal women have been clarified to include aromatase inhibitor with ovarian suppression for consistency with the National Comprehensive Cancer Network's recommendations and standard practice (Sections 3.1.1 and 4.4.2).
- The membership of the Independent Review Committee has been updated to reflect that the committee comprises of three rather than five pathologists (Sections 3.1.2 and 9.3).
- The statement that 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) treatment will be separated from pertuzumab treatment by a minimum interval of 5 weeks has been clarified to be consistent with the treatment regimen that is used in this protocol. The 5-week delay refers to the interval between the end of neoadjuvant treatment with pertuzumab and the start of adjuvant treatment with FEC (Section 3.3.3).
- The exclusion criterion for patients with a history of other malignancies has been revised to specify a 5-year window before screening to permit enrollment of patients with prior malignancies who might benefit from the study treatment (Section 4.1.2).
- The use of pharmacokinetic (PK) and HER2 extracellular domain (ECD) samples has been clarified that, although samples from patients in the pertuzumab and placebo arms will be obtained to maintain blinding to the study treatment, only samples from patients who are treated with pertuzumab will be tested (Section 4.2). Patients' treatment assignment will be unblinded for the personnel responsible to perform PK and HER2 ECD assays so they can identify the appropriate PK and HER2 ECD samples to be analyzed.
- The instructions for the calculation of the chemotherapy dosage with use of body surface area have been updated to clarify that the nomogram that is provided in Appendix 7 may but is not required to be used for the determination of body surface area. Investigators may use equivalent formulas for body surface area calculations (Section 4.3.2).
- The use of prohibited therapies has been clarified to include herbal remedies only if they are used for the treatment of cancer. This change has been made because the term herbal remedy is too general for a prohibition to be applied consistently but herbal remedy use is prohibited for the treatment of cancer (Section 4.4.3).
- Instructions have been added for patients with an allergy to magnetic resonance imaging contrast agents that cannot be managed with premedication and allows the use of ultrasound or molybdenum target mammography (Section 4.5.1.4).
- The instructions for urinalysis have been revised to allow urinalysis with a laboratory test at investigational sites that do not test with use of a dipstick (Section 4.5.1.5).
- Resection specimens for exploratory research on candidate biomarkers have been clarified and are required samples from all patients (Section 4.5.1.5).

- The requirement to further test tumor specimens from patients who do not meet the study entry eligibility criteria has been removed (Section 4.5.1.5).
- The instructions for cardiac assessments have been clarified. Only abnormal, clinically-significant ECGs should be documented on the Adverse Event electronic Case Report Form. If an abnormal ECG is not clinically significant, it does not need to be documented as an adverse event (Section 4.5.1.10).
- The observation time of patients after the first infusion of trastuzumab has been corrected to 30 minutes (Section 5.1.1.1).
- The secondary emergency medical contact for the study has been changed (Section 5.4.1).
- The timing of the efficacy analysis for assessment of tpCR, breast pathologic complete response, and response rate endpoints has been revised to occur when all patients who are eligible for surgery have completed surgical treatment with the assessment of pathological response (i.e., after surgical treatment following neoadjuvant therapy). Safety and PK endpoints will also be evaluated at this time. The rationale is to allow the primary efficacy analysis to occur at the time of data availability.
- The following types of samples that are required for all randomized patients at baseline have been clarified to exclude samples from patients who do not meet the study eligibility requirements. Patients who are not eligible for enrollment in the study will not be asked to donate blood for these analyses as indicated in the Schedule of Activities (Appendix 1) and the biomarker and PK and ATA sampling schedules (Appendix 2 and Appendix 3).

    Serum sample for HER2 ECD, HER ligands, and other exploratory biomarkers

    Serum sample for antibodies to pertuzumab

    Blood sample for clinical genotyping (optional)
- Footnotes in the Schedule of Activities has been corrected and reference to Cycle 21 has been deleted because there is no Cycle 21 in the study (Appendix 1).
- The Standardized Guideline for Surgical Sampling following Neoadjuvant Therapy has been revised to remove the statement that a more detailed description for sentinel lymph node biopsy will be described in a separate guidance document (Appendix 8). The guidance document is no longer required after Amendment 3 of this protocol and guidance is provided in Section 4.4.1.

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.

PROTOCOL AMENDMENT, VERSION 4:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.2.1: Pertuzumab Clinical Efficacy HER2-Positive Early-Stage Breast Cancer

Study WO20697 (NeoSphere) ~~i~~*wa*s a Phase II, randomized, multicenter, four-armed study to compare the safety and efficacy of trastuzumab + docetaxel (Arm A) versus pertuzumab + trastuzumab + docetaxel (Arm B) versus pertuzumab + trastuzumab (Arm C) versus pertuzumab + docetaxel (Arm D) in the neoadjuvant setting in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer….

A 5-year follow-up analysis was conducted of the prespecified secondary endpoints of PFS (defined as the time from randomization to the first documentation of progressive disease or death), disease-free survival (DFS; time from the first date of no disease [i.e., date of surgery] to the first documentation of progressive disease or death), and safety for the overall and adjuvant treatment periods (Gianni et al. 2016).

The 5-year PFS rates were 81% (95% CI: 71, 87) for Arm A, 86% (95% CI: 77, 91) for Arm B, 73% (95% CI: 64, 81) for Arm C, and 73% (95% CI: 63, 81) for Arm D (hazard ratio [HR] =0.69 [95% CI: 0.34, 1.40] Arm B vs. Arm A). The 5-year PFS rate was 85% (95% CI: 76, 91) for patients who achieved a tpCR compared with 76% (95% CI: 71, 81) for patients who did not achieve a tpCR (HR =0.54 [95% CI: 0.29, 1.00]) in all arms combined. DFS results were consistent with PFS results (Gianni et al. 2016).

No new or long-term safety concerns were identified after 5 years of follow-up. The overall tolerability profile was similar across the treatment arms and consistent with the profile that was previously reported for the neoadjuvant period without any additional or long-term cardiotoxicity (Gianni et al. 2016).

Study BO22280 (TRYPHAENA) ~~i~~*wa*s a Phase II, randomized, multicenter, multinational, three-arm study in patients with locally advanced, operable, and inflammatory (T2–4d) HER2-positive breast cancer who ~~a~~*we*re scheduled for neoadjuvant therapy. Patients ~~a~~*we*re treated with one of three treatment regimens: 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) + trastuzumab + pertuzumab followed by docetaxel + trastuzumab + pertuzumab (Arm A); FEC followed by docetaxel + trastuzumab + pertuzumab (Arm B); or docetaxel + carboplatin + trastuzumab + pertuzumab (Arm C*; Schneeweiss et al. 2011*).

All three treatment regimens ~~a~~*we*re active and the majority of patients achieved a bpCR. The bpCR (ypT0/is) rates were similar across the treatment arms for the intent-to-treat

(ITT) population (Arm A: 61.6%; Arm B: 57.3%; and Arm C: 66.2%). A similar pattern of responses was observed when other definitions of pathologic complete response (pCR) were used, such as tpCR (see Section 3.4.1.1) or German Breast Group pCR, (defined as ypT0, ypN0), except that the pCR rate decreased as the stringency of the increased definition *(Schneeweiss et al. 2013)*.

The results of Study BO22280 demonstrated that *neoadjuvant* pertuzumab ~~can be added to~~*and* trastuzumab *can be administered concurrently or sequentially* in combination with ~~commonly used anthracycline or~~*FEC-docetaxel chemotherapy or concurrently with a* carboplatin-based chemotherapy regimen~~s~~ without substantial additions to the cardiac toxicity or the adverse event burden, or interrupting or delaying the delivery of standard chemotherapy regimens with trastuzumab *(Schneeweiss et al. 2013)*.

HER2-Positive Metastatic Breast Cancer

In a Phase III study (Study WO20698/TOC4129g [CLEOPATRA]) of patients with previously-untreated HER2-positive metastatic breast cancer (MBC), a statistically-significant and clinically-meaningful improvement in PFS was observed in patients who were treated with pertuzumab + trastuzumab + docetaxel compared with patients who received placebo + trastuzumab + docetaxel. Median PFS was prolonged by 6.1 months and the risk of disease progression or death was reduced by 38% (HR = 0.62; p < 0.0001). Median PFS was 12.4 months in the control group and 18.5 months in the pertuzumab group. Secondary endpoints of investigator-assessed PFS (HR = 0.65; 95% CI: 0.54, 0.78) and objective response rate (ORR; patients who achieve a complete response [CR] or partial response [PR]; 69% vs. 80%; 95% CI: 4.2, 17.5) all supported the primary endpoint. At the second interim analysis of overall survival, a statistically-significant reduction in the risk of death was demonstrated (HR = 0.66; 95% CI: 0.52, 0.84; p = 0.0008). *At the time of the final analysis of OS, the median OS for patients in the pertuzumab-combination group was 56.5 months (95% CI: 49.3 to NR) compared with 40.8 months (95% CI, 35.8–48.3) for patients in the placebo-combination group (HR 0.68; 95% CI, 0.56-0.84; p<0.001). The analysis was not adjusted for crossover to pertuzumab (Swain et al. 2015).* These study results led to the approval of pertuzumab in combination with trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive MBC in some countries (i.e., United States and within the European Union) and this application is currently under review in other countries (Baselga et al. 2012a, 2012b).

SECTION 1.2.2.2: Pertuzumab Clinical Safety

As of ~~30 November 2013~~*7 December 2015*, ~~more than 3116~~*an estimated total of 10,215* patients with cancer ha~~ve~~*d* been treated with pertuzumab in Roche-sponsored studies. The most commonly reported adverse events in patients who received single-agent pertuzumab *(n =386)* were diarrhea, fatigue, nausea, vomiting, and decreased appetite. The majority of adverse events that were reported were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0

Grade 1 or 2 in severity and the proportion of patients across the entire pertuzumab program who discontinued study treatment as a result of an adverse event was ~~12.8%~~*low*.

Symptomatic Left Ventricular Systolic Dysfunction or Asymptomatic Decrease in Left Ventricular Ejection Fraction

Pertuzumab has not been studied in patients with a pretreatment LVEF value of ≤50%, a ~~prior~~ history of congestive heart failure, decreases in LVEF to <50% during prior trastuzumab adjuvant therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia that requires treatment, or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent.

Infusion-Associated Reactions, Hypersensitivity Reactions (Including Anaphylaxis)

In single-agent pertuzumab studies, 8 cases (2.1%) of anaphylaxis or hypersensitivity (Grades 1–4) were reported. In Study BO17929, involving patients with MBC who received pertuzumab and trastuzumab, the incidence of anaphylaxis *and hypersensitivity* was 4.8%. *All events were Grade 1 or 2 in severity.* In Study WO20697~~/TOC4129g, 0.9% of patients (1 of 107) with EBC who received pertuzumab and trastuzumab had a Grade ≥ 3 event~~*, 7%-13% in all treatment arms that included treatment with pertuzumab versus 2% in the trastuzumab +docetaxel arm had an event of anaphylaxis and/or hypersensitivity. Of these, 2 patients who received treatment with trastuzumab +pertuzumab +docetaxel (Arm B) and 3 patients who received treatment with trastuzumab +pertuzumab (Arm C) had a Grade ≥3 event.*

In Study WO20698/TOC4129g, ~~10.8~~*11.3*% of patients in the pertuzumab arm had a hypersensitivity event (Grades 1–4), compared with 9.~~1~~*3*% in the placebo arm. Overall, the reactions were mild or moderate in severity and resolved with treatment. Eight patients in the pertuzumab arm had a Grade ≥3 event. Most reactions were assessed as secondary to docetaxel infusions.

In the same study, the initial dose of pertuzumab or placebo (Day 1, Cycle 1) was administered the day before trastuzumab and docetaxel were administered to allow for the ~~examination~~*evaluation* of pertuzumab infusion–associated reactions. On Day 1, Cycle 1 (i.e., after pertuzumab only), the overall frequency of infusion-associated reactions was ~~15~~*9.8*% in the placebo arm and ~~19~~*13.2*% in the pertuzumab arm with the majority of reactions reported as mild or moderate. The most common infusion-associated reactions (≥1.~~5~~*0*%) in the pertuzumab arm were pyrexia, chills, fatigue, headache, ~~nausea~~*asthenia, hypersensitivity*, and ~~diarrhea~~*vomiting*. During Cycle 2 when all drugs were administered on the same day, the ~~incidence of adverse events was higher (34% in the placebo arm vs. 29% in the pertuzumab arm). The~~ most common infusion-associated reactions (≥1.~~5~~*0*%) in the pertuzumab arm were fatigue, drug hypersensitivity, ~~alopecia, nausea, decreased appetite, constipation, diarrhea,~~

~~stomatitis, and (this list includes events that occurred within 24 hours after the first treatment). Over all cycles, the proportion of patients who experienced at least one adverse event on the day of infusion was 83% in the pertuzumab arm compared with 79% in the placebo arm. Few patients had an adverse event that started during a pertuzumab or placebo infusion (9% in the pertuzumab arm and 5% in the placebo arm), and the majority of these events occurred in the first two cycles~~*dysgeusia, hypersensitivity, myalgia, and vomiting*.

SECTION 1.4: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Although initial safety data to date with pertuzumab in previously-untreated patients in the neoadjuvant (Gianni et al. 2012) and metastatic settings (Baselga et al. 2012a) appear acceptable, ~~a~~*the* safety monitoring plan for this study~~,~~ includ~~ing~~*es* appropriate eligibility criteria, dose modification guidelines, and ~~interim safety analyses as well as~~ regular monitoring of accumulating patient safety data by ~~a Safety Monitoring Committee,~~*the Sponsor's study team and* has been put in place to minimize any potential risk in the study patient population.

SECTION 2.3: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To analyze biomarkers in tumor tissue ~~or serum~~*taken at baseline or at the time of resection* (~~e.g.,~~*markers analyzed may include but are not limited to* HER2/3 mRNA and/or protein, PI~~3~~K*3CA*, phosphatase and tensin homolog [PTEN], *programmed death–ligand 1 [PD-L1], and cluster of differentiation 8 [CD8]), and serum (e.g.,* HER ligands~~,~~ *and* HER2 ECD) and evaluate correlations with clinical outcomes and, if applicable, safety outcomes

SECTION 3.1.1: Overview of Study Design

This is an Asia-Pacific regional, randomized, double-blind, Phase III, multicenter study to evaluate treatment with trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel in patients who are chemotherapy-naive with early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0) HER2-positive breast cancer. A primary tumor with ~~a~~*the* longest diameter of > 2 cm is required ~~for patients with early stage breast cancer~~.

Approximately 328 eligible patients will be enrolled at approximately ~~28~~*24* sites, resulting in approximately 219 patients in Arm A and 109 patients in Arm B. Randomization will be stratified by disease category (early-stage or locally advanced) and hormone-receptor status (positive for estrogen receptor [ER] and/or progesterone receptor [PgR] or negative for both).

For patients with tumors that are ER and/or PgR positive, hormonal agents (tamoxifen or an aromatase inhibitor for postmenopausal patients or tamoxifen*,* with or without *ovarian suppression, or aromatase inhibitor with* ovarian suppression for premenopausal patients) should be started at the end of FEC chemotherapy and given for at least

5 years. Radiotherapy is to be given as clinically indicated at the end of FEC chemotherapy.

Patients will be evaluated for clinical response prior to surgery (i.e., during Cycles 1–4) in accordance with RECIST v1.1. Patients will be evaluated for pathologic response after surgery and evaluated for disease recurrence. The primary efficacy objective will be evaluated when all patients *who are eligible for surgery* have completed the*ir surgical* treatment ~~completion/discontinuation visit (i.e., after completion of all neoadjuvant and adjuvant study treatment)~~*with the assessment of pathological response*. Patients will be evaluated for safety throughout the study with laboratory tests and adverse event reports. Serum samples will be collected from a subset of approximately 50 Chinese patients for characterization of pertuzumab pharmacokinetics.

SECTION 3.1.2: Independent Review Committee

An IRC that consists of independent experts who are not involved in the study (including approximately ~~five~~*three* pathologists) will evaluate the pathologic response.

SECTION 3.1.3: Safety ~~Monitoring Committee~~*Data Review*

~~A Safety Monitoring Committee (including the Sponsor's Medical Monitor, a drug safety physician, and representatives from any other function as needed and/or selected study investigators)~~ *The Sponsor's study team* will review ~~blinded~~ adverse events*, serious adverse events, and any other safety data* in the study on a regularly scheduled basis.

It is the responsibility of the ~~Safety Monitoring Committee~~*study team* to review accumulating safety data, assess and monitor ~~evolving~~*ongoing* safety ~~trends~~ of patients, evaluate potential changes to the clinical study protocol ~~(including dose modification criteria, based on available safety analyses)~~, and ultimately safeguard patient safety.

~~Details of the composition, roles, and responsibilities of the Safety Monitoring Committee will be provided in a separate charter.~~

SECTION 3.3.2: Rationale for Neoadjuvant Therapy

Adjuvant systemic therapies for breast cancer (i.e., drugs to reduce the risk of breast cancer recurrence) historically have been administered after definitive breast surgery. Preoperative or neoadjuvant systemic chemotherapy that was once reserved for patients with locally advanced breast cancer ~~in~~*for* whom the goal was to render large breast cancers operable has become increasingly common. There are several potential rationales for neoadjuvant treatment for early-stage breast cancer. Giving preoperative chemotherapy permits breast conservation in some patients who would otherwise require mastectomy and may improve cosmesis in existing candidates for breast conservation (Fisher et al. 2002; Alm El-Din and Taghian 2009). Preoperative therapy also enables the oncologist to evaluate tumor response and discontinue ineffective therapy or substitute an alternative systemic therapy. Further, a patient's response to neoadjuvant chemotherapy may provide prognostic information that can supplement

conventional prognostic data such as initial staging, tumor grade, and receptor status. Finally, the neoadjuvant setting provides investigators with the unique opportunity to examine modulation of *tumor* tissue biomarkers from the time of biopsy to the time of definitive breast surgery after completion of preoperative systemic therapy *in patients who have residual disease*.

SECTION 3.3.3: Rationale for Adjuvant Therapy

…It is possible that pertuzumab will be equally tolerable when given in combination with anthracyclines to similarly selected patients. However, in the interest of patient safety, *adjuvant* FEC treatment will be separated from *neoadjuvant* pertuzumab treatment by a minimum of 5 weeks.

SECTION 3.3.4: Rationale for Docetaxel Dosage

To increase the tolerability of the combined regimen, the ~~initial~~ dose of docetaxel used in this study will be 75 mg/m2.

SECTION 3.3.6: Rationale for Biomarker Assessments

Such molecules that are considered for analyses may include but are not limited to PTEN, PIK3CA mutations, HER3 and HER2 mRNA, *PD-L1, CD8,* and ~~protein expressions~~*other markers that are relevant to breast cancer*.

If appropriate, a refinement of the translational research plan ~~can~~*may* be implemented prior to the data cutoff date to take into account emerging data in the literature and allow for the latest state-of-the-art technology to be applied.

SECTION 3.4.3: Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Expression levels or incidence of biomarkers at baseline and *in resection specimen tissue*, *especially* for patients with residual disease, at the time of surgery (i.e., after neoadjuvant treatment) and their relationship to efficacy or safety parameters

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- HER2-positive breast cancer confirmed by a Sponsor-designated central laboratory and defined as 3+ score by IHC in $>10\%$ of immunoreactive cells or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals ≥ 2.0) by in situ hybridization (ISH)

  A tumor sample that consists of a tumor block or eight unstained, freshly cut slides must be available for central laboratory HER2 testing by IHC and ISH. Note that up to ~~seven~~*an* additional *seven* slides are required for exploratory biomarker research. *Therefore, 15 slides are requested at screening.*

SECTION 4.1.2: Exclusion Criteria

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

- History of other malignancy *within 5 years prior to screening*, except for *appropriately-treated* carcinoma in situ of the cervix ~~or squamous or basal cell~~, *non-melanoma skin* carcinoma*, or Stage I uterine cancer*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The investigator and the patient will be blinded to the treatment assignment. All other individuals who are directly involved in this study will remain blinded to the treatment assignment until completion of the primary analysis. Patient~~s~~ *treatment assignment* will not be unblinded until after the final 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.

Although PK and HER2 ECD samples must also be obtained from patients who are randomized to the placebo arm to maintain the blinding to the treatment assignment, only the PK and HER2 ECD samples from patients who are treated with pertuzumab and enrolled in the PK substudy in China will be tested. The study personnel that are responsible to perform the PK and HER2 ECD assays will be unblinded to a patient's treatment assignment to identify the appropriate PK and HER2 ECD samples to be analyzed.

SECTION 4.3.1.2: Pertuzumab and Placebo

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine-acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-mL vial (14~~.0~~ mL solution per vial) contains approximately 420 mg of pertuzumab. Pertuzumab-matching placebo has the identical formulation but does not contain the antibody.

SECTION 4.3.2.2: Docetaxel

…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~~*is* provided*, which may be used* for the determination of body surface area (see Appendix 7).

SECTION 4.3.2.4: 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy

…A nomogram ~~will be~~*is* provided*, which may be used* for the determination of body surface area (see Appendix 7).

SECTION 4.4.1: Surgery

Before the initiation of neoadjuvant treatment, the primary tumor site ~~should~~*must* be physically marked per the standard local practice (e.g., skin tattoo or surgical clip) to enable appropriate surgical excision in case of tumor regression during neoadjuvant therapy.

In the event that a biopsy of the sentinel lymph node is performed, it is recommended that both dye and~~/or~~ isotope be used. The dye and isotope should not be injected into the tumor itself because they may alter the tissue and affect the molecular analyses to be performed on the tumor tissue sample.

SECTION 4.4.2: Permitted Therapy

The following treatments are permitted during the study:

- For patients with tumors that are ER and/or PgR positive: hormonal agents (tamoxifen or an aromatase inhibitor for postmenopausal patients; tamoxifen with or without *ovarian suppression, or aromatase inhibitor with* ovarian suppression for premenopausal patients) initiated at the end of FEC chemotherapy and administered for at least 5 years
- Anti-emetic *treatment*s (e.g., approved prophylactic serotonin-antagonists~~,~~ *and* benzodiazepines~~, ondansetron~~)

SECTION 4.4.3: Prohibited Therapy

Use of the following therapies is prohibited during the treatment period of the study:

- Herbal remedies initiated ~~during the study~~*for cancer treatment*

  Other ~~H~~*h*erbal remedies ~~initiated prior to study entry and continuing during the study~~ are *discouraged but* permitted and must be reported on the appropriate eCRF.

SECTION 4.5.1.4: Tumor and Response Evaluations

The baseline breast tumor must be $>$2 cm in diameter for *all* patients ~~with early stage breast cancer~~. Baseline tumor assessments will include a breast magnetic resonance imaging (MRI) scan and a clinical breast examination (CBE; including breast, axilla, and supraclavicular fossa). *If a patient has an allergy to an MRI contrast agent that cannot be managed with premedication per standard practice, then an ultrasound or molybdenum target mammography may be used.* Disease status should also be evaluated by additional conventional methods such as mammogram, ultrasound, computed tomography (CT) scans, or X-rays per local medical practice. A baseline bone scan is mandatory. In the absence of radioactive isotopes, an MRI scan (with gadolinium enhancement if required) or positron emission tomography (PET) scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.

SECTION 4.5.1.5: Laboratory Assessments

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

- Urinalysis, ~~including~~*which may be performed by* dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination where applicable (e.g., if the ~~dipstick~~*urinalysis* result is positive, then a microscopic examination should be performed; sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria)
- Mandatory tumor tissue sample obtained at screening for prospective central determination of HER2 status by IHC and ISH *and exploratory biomarker research:*

  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 or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals ≥2.0) by ISH prior to randomization. Paraffin-embedded tumor tissue block or a partial block must be obtained. If sites are unable to send a tissue block because of local regulations, at least ~~eight~~*15* unstained, freshly cut slides should be sent for HER2 testing and ~~up to seven additional unstained slides should be sent for~~ exploratory biomarker research (see below). The slides should be cut from consecutive slices from the same block.

  After completion of HER2 testing for eligibility criteria, patient samples may also be tested with other HER2 assays to establish performance characteristics of these assays for diagnostic development *but if generated, these data will have no impact on the study eligibility of the patient.* ~~Testing could be performed on all screened patients (both patients who are enrolled and those who failed screening). These testing data will have no impact on eligibility and testing will be performed only after eligibility is established for each patient~~*Additional testing will not be performed on patients who failed screening.*

- ~~Tumor tissue resection specimen taken at the time of surgery for evaluation of tpCR and bpCR~~
- *Remaining* ~~T~~*t*umor tissue sample obtained *from enrolled patients* at screening ~~(and up to seven additional slides, as mentioned above) and residual tissue specimens taken at the time of surgery,~~*will be used* for exploratory research on candidate biomarkers; such analyses may include but will not be limited to the following: HER2/3 mRNA and/or protein, PI~~3~~K*3CA mutation*, PTEN*, PD-L1, CD8, and other biomarkers that are relevant to breast cancer*
- *Mandatory resection tissue specimen obtained at the time of surgery for determination of HER2 status and for assessment of exploratory biomarkers*

  A paraffin-embedded resection tissue block or up to 15 unstained, freshly-cut slides should be sent. The slides should be from consecutive slices from the same block.

- Optional tumor tissue and/or serum sample collection at the time of disease progression or recurrence

  A paraffin-embedded disease progression or recurrence tumor tissue block or up to 15 unstained, freshly-cut slides should be sent. The slides should be from consecutive slices from the same block.

Samples listed above will be destroyed at the end of the study, with the following exceptions:

- Tissue blocks that are submitted at baseline for eligibility screening and exploratory biomarker research will be returned in a batched manner to the sites after all patients have completed the neoadjuvant phase of the study. *All other tissue blocks that are submitted will be returned to the sites in batches at the latest 5 years after the last patient in.* 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.

SECTION 4.5.1.10: Cardiac Assessments

Electrocardiograms

Single 12-lead ECGs will be performed locally and assessed at the time of screening and otherwise as clinically indicated. ~~For safety monitoring purposes, any abnormalities on the ECGs must be documented on the Adverse Event eCRF.~~ The investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. For ECG tracings that will fade over time (e.g., ECGs on thermal paper), lasting legible copies should be filed together with the original.

SECTION 4.6.2: Study and Site Discontinuation

The Sponsor has the right to replace a site at any time. Reasons for the replacement of a site may include but are not limited to:

- *No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)*

SECTION 5.1.1.1: Infusion-Associated Reactions, Hypersensitivity Reactions (Including Anaphylaxis)

The administration of pertuzumab and trastuzumab 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 ~~90~~*30* minutes after the first~~/~~ *and* each *subsequent* trastuzumab infusion. If the pertuzumab infusion is well tolerated during Cycle 1, the observation time can be decreased to 30 minutes for subsequent infusions.

SECTION 5.2: SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and ~~non serious~~ adverse events 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.

SECTION 5.2.3: ~~Non Serious~~ Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

~~Non serious a~~*A*dverse events of special interest must 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).

SECTION 5.3.5.4: Abnormal Laboratory Test Values

Not every laboratory test result abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is clinically significant in the investigator's judgment

  Note: For oncology studies, certain abnormal values may not qualify as adverse events.

SECTION 5.3.5.5: Abnormal Vital Sign Values

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~~*(see Section 5.3.5.4 for details on recording persistent adverse events)*.

SECTION 5.3.5.6: Abnormal Liver Function Tests

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory test values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or a*n* ~~non serious~~ adverse event of special interest (see Section 5.4.2).

SECTION 5.3.5.7: Deaths

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

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

…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 *(see Section 5.4.2 for further details)*
- ~~Non serious a~~*A*dverse events of special interest *(see Section 5.4.2 for further details)*
- Pregnancies *(see Section 5.4.3 for further details)*

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Secondary Contact

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

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

SECTION 5.4.2.1: Events that Occur prior to Initiation of Study Drug

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events that are caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event/~~Non Serious~~ Adverse Event of Special Interest CRF and Fax Coversheet 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) with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Patients who undergo screening procedures but do not enroll in the study will only have serious adverse events recorded in the Roche Drug Safety database and not in the study's clinical database.

SECTION 5.4.2.2: Events that Occur after Initiation of Study Drug

After initiation of the study drug, serious adverse events and ~~non serious~~ adverse events of special interest will be reported until study completion. 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 Serious Adverse Event/~~Non Serious~~ Adverse Event of Special Interest CRF and Fax Coversheet 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) with use of 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 after study completion are provided in Section 5.6.

SECTION 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~~*Clinical Trial Pregnancy Reporting Form* should be completed ~~by the investigator~~*and submitted to the Sponsor or its designee* 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~~*, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.* Pregnancy should not be recorded on the Adverse Event eCRF….

SECTION 5.4.3.3: Abortions

Any ~~spontaneous~~ abortion should be classified as a serious adverse event (as the Sponsor considers ~~spontaneous~~ abortions to be medically significant events), 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).

SECTION 5.5.1: Investigator Follow-Up

All pregnancies that are reported during the study should be followed until the pregnancy outcome *(see Section 5.4.3)*. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

SECTION 5.5.2: Sponsor Follow-Up

For serious adverse events, ~~non-serious~~ adverse events of special interest, 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) to perform an independent medical assessment of the reported case.

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

The Sponsor will promptly evaluate all serious adverse events and ~~non-serious~~ adverse events of special interest 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.

SECTION 6.4.1: Primary Efficacy Endpoint

…The primary analysis will be performed when all patients *who are eligible for surgery* have completed the*ir surgical* treatment ~~completion/discontinuation visit~~*with an assessment of pathological response*. The analysis will be based on the ITT population with patients grouped by the treatment assigned at the time of randomization. In the ITT population, patients whose tpCR assessment is missing or invalid are counted as not achieving tpCR.

SECTION 6.4.2.6: Disease-Free Survival

Only patients who undergo surgery will be included in the analysis. It is assumed that all patients who undergo surgery are disease free and; hence, patients are known to be disease free if they have undergone surgery and no recurrence of disease is reported thereafter. ~~P~~*Data from p*atients who have not had an event at the time of the analysis will be censored as of the date they were last known to be alive and event free.
The methods for data analysis are similar to those described for EFS. Note that the analysis for DFS is exploratory because of the non-randomized patient population.

SECTION 6.4.2.7: Overall Survival

Overall survival is defined as the time from randomization to death from any cause. *Data from* ~~P~~*p*atients who are alive at the time of the analysis will be censored as of the last date they were known to be alive. The methods for data analysis are similar to those described for EFS.

SECTION 6.5: SAFETY ANALYSES

Safety analyses will be performed on the safety analysis population, which will consist of all patients who received at least one dose of study drugs and patients will be grouped by the treatment they actually received. *The safety analyses will be performed at the same time as the primary efficacy analysis, the final analyses, and when all patients have completed the treatment completion or study discontinuation visit.*

SECTION 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 ≥ 10 percentage points from baseline to an LVEF of $< 50\%$) at any time during the study will be summarized by treatment arm.

SECTION 6.7: INTERIM ANALYSES

There is no interim analysis planned for the primary efficacy outcome measure tpCR. EFS and DFS data will be summarized descriptively ~~when all patients have completed the treatment completion/discontinuation visit~~*at the time of the primary efficacy analysis*. Note that a final analysis of EFS, DFS, and overall survival will be performed at the end of the study approximately 5 years after randomization of the last patient.

SECTION 8.4: CONFIDENTIALITY

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

SECTION 9.2: *PROTOCOL DEVIATIONS*

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB and/or EC in accordance with established IRB and/or EC policies and procedures.

SECTION 9.4: ADMINISTRATIVE STRUCTURE

An IRC that consists of independent experts who are not involved in the study (including approximately ~~five~~*three* pathologists) will evaluate pathologic response. The details of the composition, roles, and responsibilities of the IRC will be provided in a charter.

~~A Safety Monitoring Committee (including the Sponsor's Medical Monitor, a drug safety physician, and representatives from any other function as needed and/or selected study investigators) will review adverse events in the study on a regularly scheduled basis. The details of the composition, roles, and responsibilities of the Safety Monitoring Committee will be provided in a charter.~~

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:
http://www.roche.com/dam/jcr:1c46aa73-cea0-4b9b-8eaa-e9a788ed021b/en/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific meetings. *For all clinical studies conducted in patients that involve an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies conducted in patients that involve an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.*

~~If this is foreseen, t~~*T*he investigator *must* agree~~s~~ to submit all manuscripts or abstracts to the Sponsor prior to submission *for publication or presentation*. This allows the Sponsor to protect proprietary information and 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 the publication of study results.~~ In accordance with standard editorial and ethical practice, the Sponsor will generally support only publication of multicenter studies in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

TABLE 2: Adverse Event Severity Grading Scale ***for Events Not Specifically Listed in NCI CTCAE***

Only the title for Table 2 has been revised.

APPENDIX 1: Schedule of Activities

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Biomarker and Pharmacokinetic Activities

Appendix 2 has been revised to change screening visit to baseline visit.

APPENDIX 3: Schedule of Anti-Therapeutic Antibody Activities

Appendix 3 has been revised to change screening visit to baseline visit.

APPENDIX 8: Standardized Guideline for Surgical Sampling following Neoadjuvant Therapy

All identified axillary lymph nodes should be sent for histologic examination. ~~A more detailed description for sentinel lymph node biopsy will be described in a separate guidance document.~~

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDY EVALUATING PERTUZUMAB IN COMBINATION WITH DOCETAXEL AND TRASTUZUMAB AS NEOADJUVANT THERAPY, AND PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AS ADJUVANT THERAPY FOLLOWING SURGERY AND CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE OR LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	YO28762
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], M.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 return the original of the form to your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III STUDY EVALUATING PERTUZUMAB IN COMBINATION WITH DOCETAXEL AND TRASTUZUMAB AS NEOADJUVANT THERAPY, AND PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AS ADJUVANT THERAPY FOLLOWING SURGERY AND CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE OR LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	YO28762
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
TEST PRODUCT:	Pertuzumab (RO4368451)
PHASE:	III
INDICATION:	HER2-positive breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel as neoadjuvant treatment prior to surgery in patients who are chemotherapy-naive with early-stage or locally advanced human epidermal growth factor receptor 2 (HER2)–positive breast cancer as measured by total pathologic complete response (tpCR) rate as assessed by an Independent Review Committee (IRC)

The secondary efficacy objectives for this study are to evaluate the efficacy of trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel as neoadjuvant treatment prior to surgery in patients with early-stage or locally advanced HER2-positive breast cancer as measured by the following:

- tpCR rate assessed by the local pathologist
- Breast pathologic complete response (bpCR) rate assessed by the IRC
- bpCR rate assessed by the local pathologist
- Clinical response rates during Cycles 1–4 in accordance with Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
- Event-free survival (EFS)
- Disease-free survival (DFS)
- Overall survival

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of each treatment regimen

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore relationships between findings from the sentinel lymph node (SLN) biopsy tissue samples (if biopsy is performed) and the axillary lymph node dissection (ALND) tissue sample from the surgery undertaken after neoadjuvant treatment
- To characterize the pharmacokinetics of pertuzumab after intravenous (IV) infusion in a subset of Chinese patients with early-stage or locally advanced HER2-positive breast cancer
- To analyze biomarkers in tumor tissue *taken at baseline or at the time of resection* (*markers analyzed may include but are not limited to* HER2/3 mRNA and/or protein, PIK*3CA*, phosphatase and tensin homolog, *programmed death–ligand 1, and cluster of differentiation 8), and serum (e.g.,* HER ligands *and* HER2 extracellular domain [ECD]) and evaluate correlations with clinical outcomes and, if applicable, safety outcomes
- To analyze the effect of HER2 ECD on pharmacokinetics of pertuzumab
- To analyze the effect of anti-therapeutic antibodies (ATAs) on pharmacokinetics, safety, and efficacy
- To assess tpCR in relation to clinical response rate, EFS, DFS, and overall survival

Study Design

Description of Study

This is an Asia-Pacific regional, randomized, double-blind, Phase III, multicenter study to evaluate treatment with trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel in patients who are chemotherapy-naive with early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0) HER2-positive breast cancer. A primary tumor with *the* longest diameter of > 2 cm is required.

Patients will be randomized in a 2:1 ratio to Arm A or Arm B, respectively, and treated every 3 weeks for four cycles prior to surgery as follows:

- Arm A

  Trastuzumab (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for Cycles 2–4)
  Pertuzumab (840-mg loading dose for Cycle 1, followed by 420 mg for Cycles 2–4)
  Docetaxel (75 mg/m^2 for Cycles 1–4)
- Arm B

  Trastuzumab (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for Cycles 2–4)
  Placebo (Cycles 1–4)
  Docetaxel (75 mg/m^2 for Cycles 1–4)

After completing four cycles of neoadjuvant treatment, all patients who are eligible for surgery will undergo surgery and have their pathologic response evaluated. After surgery, patients will receive 500–600 mg/m^2 5-fluorouracil (5-FU), 90–120 mg/m^2 epirubicin, and 500–600 mg/m^2 cyclophosphamide (FEC) every 3 weeks for three cycles (Cycles 5–7). Patients will then continue HER2-targeted therapy in accordance with the initial randomization every 3 weeks until disease recurrence (as assessed by the investigator) or unacceptable toxicity for up to 1 year total (17 cycles with inclusion of four cycles in the neoadjuvant setting) as follows:

- Arm A

  Trastuzumab (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9–20)
  Pertuzumab (840-mg loading dose for Cycle 8, followed by 420 mg for Cycles 9–20)

- Arm B

  Trastuzumab (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9–20)
  Placebo (Cycles 8–20)

For patients with tumors that are estrogen receptor (ER) and/or progesterone receptor (PgR) positive, hormonal agents (tamoxifen or an aromatase inhibitor for postmenopausal patients or tamoxifen*,* with or without *ovarian suppression, or aromatase inhibitor with* ovarian suppression for premenopausal patients) should be started at the end of FEC chemotherapy and given for at least 5 years. Radiotherapy is to be given as clinically indicated at the end of FEC chemotherapy.

Patients who discontinue neoadjuvant (preoperative) HER2-targed therapy as a result of toxicity and patients who are not eligible for surgery will be managed as per local practice. Patients who discontinue adjuvant (postoperative) chemotherapy as a result of chemotherapy-related toxicity will continue with HER2-targeted therapy until they have received a total of 17 cycles of treatment. Approximately 28 days after the last dose of study treatment, a final safety assessment will be performed before a patient enters long-term safety follow up. Patients will be followed for disease recurrence and survival or until 5 years after randomization of the last patient.

Patients will be evaluated for clinical response prior to surgery (i.e., during Cycles 1–4) in accordance with RECIST v1.1. Patients will be evaluated for pathologic response after surgery and evaluated for disease recurrence. The primary efficacy objective will be evaluated when all patients *who are eligible for surgery* have completed the*ir surgical* treatment *with the assessment of pathological response*. Patients will be evaluated for safety throughout the study with laboratory tests and adverse event reports. Serum samples will be collected from a subset of approximately 50 Chinese patients for characterization of pertuzumab pharmacokinetics.

Number of Patients

Approximately 328 eligible patients will be enrolled at approximately *24* sites, resulting in approximately 219 patients in Arm A and 109 patients in Arm B. Randomization will be stratified by disease category (early-stage or locally advanced) and hormone-receptor status (positive for ER and/or PgR or negative for both).

Target Population

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- Breast cancer that meets the following criteria:

  Histologically confirmed invasive breast carcinoma with a primary tumor size of $>$ 2 cm by standard local assessment technique

  Stage at presentation: early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0)
- HER2-positive breast cancer confirmed by a Sponsor-designated central laboratory and defined as 3+ score by immunohistochemistry (IHC) in $>$ 10% of immunoreactive cells or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals $\geq$ 2.0) by in situ hybridization (ISH)

  A tumor sample that consists of a tumor block or eight unstained, freshly cut slides must be available for central laboratory HER2 testing by IHC and ISH. Note that up to *an* additional *seven* slides are required for exploratory biomarker research. *Therefore, 15 slides are requested at screening.*
- Known hormone receptor status (ER and PgR)
- Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$ 1
- Completion of all necessary baseline laboratory and radiologic investigations prior to randomization
- Baseline left ventricular ejection fraction (LVEF) $\geq$ 55% measured by echocardiography (ECHO; preferred) or multiple-gated acquisition (MUGA) scan

- For women who are not postmenopausal ($\geq$ 12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use one highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception during the treatment period and for at least 7 months after the last dose of study treatment
- For men: agreement to use reliable and effective contraceptive measures during the treatment period and for at least 7 months after the last dose of study treatment
- Able to comply with the study protocol in the investigator's judgment

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

- Stage IV (metastatic) breast cancer
- Inflammatory breast cancer
- Previous anti-cancer therapy or radiotherapy for any malignancy
- History of other malignancy *within 5 years prior to screening*, except for *appropriately-treated* carcinoma in situ of the cervix*, non-melanoma skin* carcinoma*, or Stage I uterine cancer*
- Concurrent anti-cancer treatment in another investigational study, including hormone therapy, bisphosphonate therapy, or immunotherapy
- Major surgical procedure that is unrelated to breast cancer within 4 weeks prior to randomization or from which the patient has not fully recovered
- Serious cardiac illness or medical condition including but not limited to the following:

  History of documented heart failure or systolic dysfunction (LVEF $<$ 50%)

  High-risk uncontrolled arrhythmia, such as atrial tachycardia with a heart rate $>$ 100 bpm at rest, significant ventricular arrhythmia (e.g., ventricular tachycardia), or higher-grade atrioventricular (AV) block (i.e., Mobitz II second-degree AV block or third-degree AV block)

  Angina pectoris requiring anti-angina medication

  Clinically-significant valvular heart disease

  Evidence of transmural infarction on ECG

  Poorly-controlled hypertension (systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 100 mmHg)
- Other concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness
- Any of the following abnormal laboratory test results immediately prior to randomization:

  Total bilirubin $>$ 1.5 $\times$ upper limit of normal (ULN) or, for cases of known Gilbert's syndrome, total bilirubin $>$ 2 $\times$ ULN

  AST and/or ALT $>$ 1.25 $\times$ ULN

  Alkaline phosphatase $>$ 2.5 $\times$ ULN

  Serum creatinine $>$ 1.5 $\times$ ULN

  Total WBC count $<$ 2500 cells/μL

  Absolute neutrophil count $<$ 1500 cells/μL

  Platelet count $<$ 100,000 cells/μL
- Sensitivity to any of the study medications, any of the ingredients or excipients of these medications, or benzyl alcohol
- Pregnant or lactating

  A negative serum pregnancy test result is required for all women who are not postmenopausal ($\geq$ 12 months of amenorrhea).

Length of Study

Recruitment is expected to last approximately 13 months. On the basis of a treatment length of 17 months for each patient, the analysis of the primary efficacy outcome measure, tpCR, will take place approximately 30 months after randomization of the first patient, when all patients have completed the treatment completion/discontinuation visit.

Approximately 28 days after the last dose of study treatment, a final safety assessment will be performed before a patient enters long-term safety follow-up. Patients will be followed for disease recurrence and survival or until 5 years after randomization of the last patient.

End of Study

The study will formally end approximately 5 years after the date of randomization of the last patient.

Efficacy Outcome Measures

The primary efficacy outcome measure is tpCR, defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes after completion of neoadjuvant therapy and surgery (i.e., ypT0/is, ypN0 in accordance with the current American Joint Committee on Cancer [AJCC] staging system) as assessed by the IRC.

The secondary efficacy outcome measures are as follows:

- tpCR assessed by local pathologist
- bpCR defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen after completion of neoadjuvant therapy and surgery (i.e., ypT0/is in accordance with the current AJCC staging system) as assessed by the IRC
- bpCR assessed by local pathologist
- Clinical response during Cycles 1−4, in accordance with RECIST v1.1
- EFS defined as time from randomization to the first documentation of one of the following events:
    - Disease progression (before surgery) as determined by the investigator with use of RECIST v1.1
        - Any evidence of in situ contralateral disease will not be identified as progressive disease (PD).
        - Any evidence of invasive contralateral disease will be considered disease progression
    - Disease recurrence (local, regional, distant, or contralateral) after surgery
    - Death from any cause
- DFS defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of one of the following events:
    - Disease recurrence (local, regional, distant, or contralateral) after surgery
    - Death from any cause
- Overall survival defined as the time from randomization to death from any cause

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events and serious adverse events
- Incidence of symptomatic left ventricular systolic dysfunction (heart failure) defined as the occurrence of symptomatic LVEF decrease or definite or probable cardiac death
- Incidence of asymptomatic decline in LVEF, defined as an absolute decrease of ≥ 10 percentage points from baseline to an LVEF of $< 50\%$
- LVEF values over the course of the study
- Laboratory test result abnormalities

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- To explore relationships between pathology findings from the SLN biopsy tissue sample, if biopsy is performed, and the ALND tissue sample, from the surgery undertaken after neoadjuvant treatment
- Observed pertuzumab concentrations at all specified pharmacokinetic (PK) sampling timepoints
- Observed pertuzumab concentrations compared with concentrations in Caucasian patients with HER2-positive breast cancer from other studies
- Observed pertuzumab concentrations during neoadjuvant treatment compared with concentrations during adjuvant treatment (postoperative)
- Expression levels or incidence of biomarkers at baseline and *in resection specimen tissue*, *especially* for patients with residual disease, at the time of surgery (i.e., after neoadjuvant treatment) and their relationship to efficacy or safety parameters
- To analyze the effect of HER2 ECD on pharmacokinetics of pertuzumab
- Incidence of ATAs and relationship with PK, safety, and efficacy outcome measures
- tpCR in relation to clinical response, EFS, DFS, and overall survival

Investigational Medicinal Products

Trastuzumab, pertuzumab, and placebo are investigational medicinal products (IMPs) in this study. Depending on local legislation, docetaxel may also be considered an IMP in this study. Where permitted by regulatory requirements, sites will obtain and utilize commercially available docetaxel. Treatments will be administered on Day 1 of each specified cycle.

All patients will receive docetaxel and trastuzumab by intravenous (IV) infusion in 3-week cycles as follows:

- Neoadjuvant treatment (prior to surgery)

  Trastuzumab (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for Cycles 2–4)

  Docetaxel (75 mg/m^2 for Cycles 1–4)
- Adjuvant treatment (after surgery and three cycles of FEC chemotherapy)

  Trastuzumab (8-mg/kg loading dose for Cycle-8, followed by 6 mg/kg for Cycles 9–20)

Test Product

Patients in Arm A will receive pertuzumab by IV infusion in 3-week cycles as follows:

- Neoadjuvant treatment (prior to surgery)

  Pertuzumab (840-mg loading dose for Cycle 1, followed by 420 mg for Cycles 2–4)
- Adjuvant treatment (after surgery and three cycles of FEC chemotherapy)

  Pertuzumab (840-mg loading dose for Cycle 8, followed by 420 mg for Cycles 9–20)

Comparator

Patients in Arm B will receive placebo by IV infusion in 3-week cycles as neoadjuvant treatment (Cycles 1–4) and as adjuvant treatment (Cycles 8–20).

Non-Investigational Medicinal Products

5-fluorouracil (5-FU), 90–120 mg/m^2 epirubicin, and 500–600 mg/m^2 cyclophosphamide are non-investigational medicinal products (non-IMPs) in this study. Depending on local legislation, docetaxel may also be considered a non-IMP in this study. After surgery, all patients will receive FEC (5-FU 500–600 mg/m^2, epirubicin 90–120 mg/m^2, and cyclophosphamide 500–600 mg/m^2) by IV infusion every 3 weeks for three cycles (Cycles 5–7).
FEC chemotherapeutic agents will be administered on Day 1 of each specified cycle.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is tpCR, defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes after completion of neoadjuvant therapy and surgery (i.e., ypT0/is, ypN0 in accordance with the current AJCC staging system) as assessed by the IRC. The primary analysis will be performed when all patients *who are eligible for surgery* have completed the*ir surgical* treatment *with an assessment of pathological response*. The analysis will be based on the intent-to-treat (ITT) population with patients grouped by treatment assigned at the time of randomization. In the ITT population, patients whose tpCR assessment is missing or invalid are counted as not achieving tpCR.

The tpCR rate as assessed by the IRC will be summarized for each treatment arm, and 95% CIs will be calculated using the Clopper-Pearson method. The two-sided Cochran-Mantel-Haenszel test, stratified by disease category (early-stage; locally advanced) and hormone receptor status (positive for ER and/or PgR; negative for both) will be used to compare the tpCR rate between the two treatment arms. An unadjusted Fisher exact test result will also be provided. Finally, the difference in tpCR rate and associated 95% CIs will be provided with use of the Hauck-Anderson method.

Determination of Sample Size

A total of 328 patients will be randomized into the study in a ratio of 2:1 to pertuzumab (Arm A) or placebo (Arm B), respectively. This will provide 85% power to detect an absolute increase in tpCR rate of 15% in the pertuzumab arm compared with the placebo arm at a two-sided significance level of 5%, assuming the tpCR rate is 20% in the placebo arm.

Secondary Analyses

The secondary efficacy outcome measures in this study are tpCR as assessed by the local pathologist, bpCR as assessed by the IRC, bpCR as assessed by the local pathologist, clinical response, EFS, DFS, and overall survival.

Safety Analyses

Safety analyses will be performed on the safety analysis population, which will consist of all patients who received at least one dose of study drugs and patients will be grouped by the treatment they actually received. *The safety analyses will be performed at the same time as the primary efficacy analysis, the final analyses, and when all patients have completed the treatment completion or study discontinuation visit.*

Exploratory Analyses

Exploratory analyses in this study are pharmacokinetic analyses, sensitivity and subgroup analyses, biomarker analyses, and anti-therapeutic antibody analyses.

Interim Analyses

There is no interim analysis planned for the primary efficacy outcome measure, tpCR. EFS and DFS data will be summarized descriptively *at the time of the primary efficacy analysis*. Note that a final analysis of EFS, DFS, and overall survival will be performed at the end of the study, approximately 5 years after randomization of the last patient.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AJCC	American Joint Committee on Cancer
ALND	axillary lymph node dissection
ATA	anti-therapeutic antibody
AV	atrioventricular
bpCR	breast pathologic complete response
CBE	clinical breast examination
CD8	*cluster of differentiation 8*
CR	complete response
C_{max}	maximum concentration
C_{min}	minimum concentration
CT	computed tomography
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DFS	disease-free survival
EBC	early breast cancer
EC	Ethics Committee
ECD	extracellular domain
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
ER	estrogen receptor
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
G-CSF	granulocyte colony-stimulating factor
HER	human epidermal growth factor receptor
HR	hazard ratio
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	investigational medicinal product
IRB	Institutional Review Board
IRC	Independent Review Committee
ISH	in situ hybridization

Abbreviation	Definition
ITT	intent to treat
IV	intravenous
IxRS	interactive voice/Web–based response system
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NYHA	*New York Heart Association*
ORR	objective response rate
pCR	pathologic complete response
PD	progressive disease
PD-L1	*programmed death–ligand 1*
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PR	partial response
PVC	polyvinyl chloride
RECIST	Response Evaluation Criteria in Solid Tumors
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
tpCR	total pathologic complete response
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. 2008). In Asia, 528,927 new breast cancer cases were diagnosed in 2008 (Ferlay et al. 2008). In China, incidence of breast cancer is increasing with nearly 170,000 new cases reported in 2008 compared with 126,000 cases in 2002 (Ferlay et al. 2002, 2008). In addition, in China, breast cancer accounts for 16.81% of all female cancers; the incidence rate of female breast cancer was 42.55 per 100,000 in 2009 and after standardizing for age in China and the rest of the world, these rates were 23.16 per 10,000 and 28.99 per 100,000, respectively (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. 2008).

Overexpression of human epidermal growth factor receptor 2 (HER2, also known as erbB2, neu, and $p185^{HER2}$) or HER2 gene amplification has been observed in approximately 10%–34% of invasive human breast cancer (Ross 2009). In China, the number of cases that were HER2 positive (2+/3+) was 42.6% (1342 of 3149 cases) as detected by fluorescence in situ hybridization and 46.9% (1477 of 3149 cases) by immunohistochemistry (IHC; Xiao Hong et al. 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). Patients with breast cancers that overexpress HER2 have been shown to have better outcomes when treated with the monoclonal antibody Herceptin® (trastuzumab) with an improvement of 4-year progression-free survival (PFS) from 67.1% to 85.3% and absolute survival rate at 4 years from 86.6% to 91.4% (Slamon et al. 2001; Romond et al. 2005). Trastuzumab binds to the juxtamembrane epitope (domain IV) of the HER2 extracellular domain (ECD) and thereby prevents cleavage and signal transduction. Trastuzumab is registered in many countries for the adjuvant treatment of breast cancer.

1.2 BACKGROUND ON PERTUZUMAB

Pertuzumab (rhuMab 2C4) is a humanized monoclonal antibody that is based on the human IgG1 framework sequences and consists of two heavy chains (449 amino acid residues) and two light chains (214 residues). Pertuzumab binds to the dimerization epitope of the HER2 receptor, and thereby inhibits dimerization of HER2 with HER2 and other HER family receptors, which in turn inhibits downstream signaling pathways. In addition to blocking signal transduction, pertuzumab is capable of inducing antibody-dependent cell-mediated cytotoxicity. Pertuzumab and trastuzumab bind to

distinct epitopes on the HER2 receptor (pertuzumab, subdomain 2; trastuzumab, subdomain 4) without competing with each other and have complementary mechanisms for disrupting HER2 signaling, which results in augmented anti-proliferative activity in vitro and in vivo when administered in combination.

1.2.1 Nonclinical Experience with Pertuzumab

Pertuzumab showed activity in xenograft models of various tumor origins such as breast, lung, and prostate cancer. In addition, pertuzumab demonstrated synergistic anti-tumor activity in combination with trastuzumab in HER2-positive breast, lung, and gastric cancer xenograft models.

Teratology findings in the nonclinical reprotoxicity study in cynomolgus monkeys showed embryo or fetal losses, low-volume amniotic fluid (oligohydramnios), and microscopic evidence of delayed renal development (renal hypoplasia) in all pertuzumab-treated groups. These findings were consistent with evidence that antibodies can be transported across the placenta during the period of organogenesis in the cynomolgus monkey.

See the Pertuzumab Investigator's Brochure for details on nonclinical studies.

1.2.2 Clinical Experience with Pertuzumab

1.2.2.1 Pertuzumab Clinical Efficacy

HER2-Positive Early-Stage Breast Cancer

Study WO20697 (NeoSphere) was a Phase II, randomized, multicenter, four-armed study to compare the safety and efficacy of trastuzumab + docetaxel (Arm A) versus pertuzumab + trastuzumab + docetaxel (Arm B) versus pertuzumab + trastuzumab (Arm C) versus pertuzumab + docetaxel (Arm D) in the neoadjuvant setting in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer. The study met its primary efficacy endpoint and demonstrated a significantly higher breast pathologic complete response (bpCR; defined as ypT0/is in accordance with the American Joint Committee on Cancer [AJCC] staging system; see Section 3.4.1.2) rate for Arm B of 45.8% compared with Arm A (29%) and Arm D (24%). The bpCR rate for Arm C was 17% and demonstrated that the two antibodies (pertuzumab and trastuzumab) administered without chemotherapy are active but significantly less than in combination with docetaxel (Arm B). The total pathologic complete response (tpCR, defined as ypT0/is, ypN0) rates were 21.5% for Arm A, 39.3% for Arm B, 11.2% for Arm C, and 17.7% for Arm D (Gianni et al. 2012).

A 5-year follow-up analysis was conducted of the prespecified secondary endpoints of PFS (defined as the time from randomization to the first documentation of progressive disease or death), disease-free survival (DFS; time from the first date of no disease [i.e., date of surgery] to the first documentation of progressive disease or death), and safety for the overall and adjuvant treatment periods (Gianni et al. 2016).

The 5-year PFS rates were 81% (95% CI: 71, 87) for Arm A, 86% (95% CI: 77, 91) for Arm B, 73% (95% CI: 64, 81) for Arm C, and 73% (95% CI: 63, 81) for Arm D (hazard ratio [HR] =0.69 [95% CI: 0.34, 1.40] Arm B vs. Arm A). The 5-year PFS rate was 85% (95% CI: 76, 91) for patients who achieved a tpCR compared with 76% (95% CI: 71, 81) for patients who did not achieve a tpCR (HR =0.54 [95% CI: 0.29, 1.00]) in all arms combined. DFS results were consistent with PFS results (Gianni et al. 2016).

No new or long-term safety concerns were identified after 5 years of follow-up. The overall tolerability profile was similar across the treatment arms and consistent with the profile that was previously reported for the neoadjuvant period without any additional or long-term cardiotoxicity (Gianni et al. 2016).

Study BO22280 (TRYPHAENA) *wa*s a Phase II, randomized, multicenter, multinational, three-arm study in patients with locally advanced, operable, and inflammatory (T2–4d) HER2-positive breast cancer who *we*re scheduled for neoadjuvant therapy. Patients *we*re treated with one of three treatment regimens: 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC)+trastuzumab+pertuzumab followed by docetaxel+trastuzumab+pertuzumab (Arm A); FEC followed by docetaxel+trastuzumab+pertuzumab (Arm B); or docetaxel+carboplatin+trastuzumab+pertuzumab (Arm C*; Schneeweiss et al. 2011*).

All three treatment regimens *we*re active and the majority of patients achieved a bpCR. The bpCR (ypT0/is) rates were similar across the treatment arms for the intent-to-treat (ITT) population (Arm A: 61.6%; Arm B: 57.3%; and Arm C: 66.2%). A similar pattern of responses was observed when other definitions of pathologic complete response (pCR) were used, such as tpCR (see Section 3.4.1.1) or German Breast Group pCR, (defined as ypT0, ypN0), except that the pCR rate decreased as the stringency of the increased definition *(Schneeweiss et al. 2013)*.

The results of Study BO22280 demonstrated that *neoadjuvant* pertuzumab *and* trastuzumab *can be administered concurrently or sequentially* in combination with *FEC-docetaxel chemotherapy or concurrently with a* carboplatin-based chemotherapy regimen without substantial additions to the cardiac toxicity or the adverse event burden, or interrupting or delaying the delivery of standard chemotherapy regimens with trastuzumab *(Schneeweiss et al. 2013)*.

In addition, a Phase III, randomized, multicenter, double-blind, placebo-controlled comparison (Study BIG 4-11/BO25126/TOC4939g [APHNITY]) of chemotherapy+trastuzumab+placebo versus chemotherapy+trastuzumab+pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer is ongoing.

HER2-Positive Metastatic Breast Cancer

In a Phase III study (Study WO20698/TOC4129g [CLEOPATRA]) of patients with previously-untreated HER2-positive metastatic breast cancer (MBC), a statistically-significant and clinically-meaningful improvement in PFS was observed in patients who were treated with pertuzumab + trastuzumab + docetaxel compared with patients who received placebo + trastuzumab + docetaxel. Median PFS was prolonged by 6.1 months and the risk of disease progression or death was reduced by 38% (HR = 0.62; p < 0.0001). Median PFS was 12.4 months in the control group and 18.5 months in the pertuzumab group. Secondary endpoints of investigator-assessed PFS (HR = 0.65; 95% CI: 0.54, 0.78) and objective response rate (ORR; patients who achieve a complete response [CR] or partial response [PR]; 69% vs. 80%; 95% CI: 4.2, 17.5) all supported the primary endpoint. At the second interim analysis of overall survival, a statistically-significant reduction in the risk of death was demonstrated (HR = 0.66; 95% CI: 0.52, 0.84; p = 0.0008). *At the time of the final analysis of OS, the median OS for patients in the pertuzumab-combination group was 56.5 months (95% CI: 49.3 to NR) compared with 40.8 months (95% CI, 35.8–48.3) for patients in the placebo-combination group (HR 0.68; 95% CI, 0.56-0.84; p<0.001). The analysis was not adjusted for crossover to pertuzumab (Swain et al. 2015).* These study results led to the approval of pertuzumab in combination with trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive MBC in some countries (i.e., United States and within the European Union) and this application is currently under review in other countries (Baselga et al. 2012a, 2012b).

1.2.2.2 Pertuzumab Clinical Safety

As of *7 December 2015, an estimated total of 10,215* patients with cancer ha*d* been treated with pertuzumab in Roche-sponsored studies. The most commonly reported adverse events in patients who received single-agent pertuzumab *(n =386)* were diarrhea, fatigue, nausea, vomiting, and decreased appetite. The majority of adverse events that were reported were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 Grade 1 or 2 in severity and the proportion of patients across the entire pertuzumab program who discontinued study treatment as a result of an adverse event was *low*.

The combination of pertuzumab, trastuzumab, and chemotherapy has been evaluated in multiple studies of patients with HER2-positive breast cancer. In a Phase II study (Study WO20697; NeoSphere) of treatment with neoadjuvant pertuzumab in patients with HER2-positive early breast cancer (EBC), the safety analysis for the neoadjuvant treatment period showed that the tolerability of pertuzumab + trastuzumab + docetaxel was acceptable, acknowledging that only four cycles of therapy were administered. The adverse events that occurred the most frequently in the neoadjuvant period (in at least 25% of patients in any arm) were alopecia, neutropenia, diarrhea, nausea, fatigue, rash, and mucosal inflammation. Of these events, alopecia and neutropenia were almost absent in Arm C (pertuzumab + trastuzumab) and the rates for many other adverse events were also reduced in this arm. The majority of Grade ≥ 3 adverse events were

blood and lymphatic system disorders (neutropenia, leukopenia, and febrile neutropenia), the rates of severe (Grade ≥3) neutropenia for trastuzumab+docetaxel and for pertuzumab+trastuzumab+docetaxel were 57.0% and 44.9%, respectively, with corresponding rates of febrile neutropenia of 7.5% and 8.5%, respectively. In the principal arms of the study (Arm A [trastuzumab+docetaxel] and Arm B [pertuzumab+trastuzumab+docetaxel]), there was no substantial difference in the occurrence of symptomatic left ventricular systolic dysfunction (LVSD) or decrease in left ventricular ejection fraction (LVEF). The combination of trastuzumab, pertuzumab, and docetaxel was generally well tolerated with no new safety signals that were identified (Gianni et al. 2012).

The safety analysis for Study BO22280 showed that the combination of pertuzumab with trastuzumab and standard anthracycline-based or non–anthracycline-based chemotherapy was generally well tolerated and resulted in no new safety signals. The cardiac safety outcomes were similar across all three arms of the study in both the anthracycline-based and non–anthracycline-based regimens. Nearly all patients (96%–100%) had an adverse event (all grades) during the neoadjuvant period. The most common adverse event in the neoadjuvant period was diarrhea (61%–72% of patients). Other common adverse events (>20% incidence in any arm) included alopecia, nausea, neutropenia, vomiting, fatigue, anemia, mucosal inflammation, constipation, dyspepsia, leukopenia, decreased appetite, and headache. Grade ≥3 events were predominately blood and lymphatic system disorders. Across Arms A, B, and C, rates of Grade ≥3 neutropenia were seen at 47.2%, 42.7%, and 46.1% and febrile neutropenia at 18.1%, 9.3% and 17.1%, respectively, and are consistent with the established profiles of the chemotherapy regimens (Schneeweiss et al. 2011).

In the Phase III study (Study WO20698/TOC4129g) of patients with previously untreated HER2-positive MBC, the regimen of pertuzumab+trastuzumab+docetaxel had a toxicity profile including cardiac toxicity that was comparable to the regimen of placebo+trastuzumab+docetaxel. The most common adverse events were alopecia (an adverse event associated with docetaxel), diarrhea, neutropenia, nausea, fatigue, and rash. Diarrhea, rash, mucosal inflammation, febrile neutropenia, dry skin, and pruritus of all grades had an increased incidence of at least 5% in the pertuzumab arm. The only Grade ≥3 adverse event that occurred at a higher incidence (>5% difference) in the pertuzumab arm than in the placebo arm was febrile neutropenia (13.8% vs. 7.6%, respectively; Baselga et al. 2012a).

Symptomatic Left Ventricular Systolic Dysfunction or Asymptomatic Decrease in Left Ventricular Ejection Fraction

Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab. In Study WO20698/TOC4129g, pertuzumab+trastuzumab+docetaxel was not associated with increases in the incidence of symptomatic LVSD or with decreases in LVEF compared with placebo+trastuzumab+docetaxel. However, patients who

received prior anthracyclines or radiotherapy to the chest area may be at a higher risk of decreased LVEF (Portera et al. 2008).

Pertuzumab has not been studied in patients with a pretreatment LVEF value of ≤50%, a history of congestive heart failure, decreases in LVEF to <50% during prior trastuzumab adjuvant therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia that requires treatment, or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent.

Infusion-Associated Reactions, Hypersensitivity Reactions (Including Anaphylaxis)

In single-agent pertuzumab studies, 8 cases (2.1%) of anaphylaxis or hypersensitivity (Grades 1–4) were reported. In Study BO17929, involving patients with MBC who received pertuzumab and trastuzumab, the incidence of anaphylaxis *and hypersensitivity* was 4.8%. *All events were Grade 1 or 2 in severity.* In Study WO20697*, 7%-13% in all treatment arms that included treatment with pertuzumab versus 2% in the trastuzumab +docetaxel arm had an event of anaphylaxis and/or hypersensitivity. Of these, 2 patients who received treatment with trastuzumab +pertuzumab +docetaxel (Arm B) and 3 patients who received treatment with trastuzumab +pertuzumab (Arm C) had a Grade ≥3 event.*

In Study WO20698/TOC4129g, *11.3*% of patients in the pertuzumab arm had a hypersensitivity event (Grades 1–4), compared with 9.*3*% in the placebo arm. Overall, the reactions were mild or moderate in severity and resolved with treatment. Eight patients in the pertuzumab arm had a Grade ≥3 event. Most reactions were assessed as secondary to docetaxel infusions.

In the same study, the initial dose of pertuzumab or placebo (Day 1, Cycle 1) was administered the day before trastuzumab and docetaxel were administered to allow for the *evaluation* of pertuzumab infusion–associated reactions. On Day 1, Cycle 1 (i.e., after pertuzumab only), the overall frequency of infusion-associated reactions was *9.8*% in the placebo arm and *13.2*% in the pertuzumab arm with the majority of reactions reported as mild or moderate. The most common infusion-associated reactions (≥1.*0*%) in the pertuzumab arm were pyrexia, chills, fatigue, headache, *asthenia, hypersensitivity*, and *vomiting*. During Cycle 2 when all drugs were administered on the same day, the most common infusion-associated reactions (≥1.*0*%) in the pertuzumab arm were fatigue, drug hypersensitivity, *dysgeusia, hypersensitivity, myalgia, and vomiting*.

1.2.2.3 Immunogenicity

The immunogenicity of pertuzumab has been assessed with use of validated bridging immunoassay methods that are designed to detect and confirm the presence of anti-therapeutic antibodies (ATAs) to pertuzumab. In Study WO20698/TOC4129g,

6.7% of patients in the placebo arm and 3.3% of patients in the pertuzumab arm tested positive for ATAs at some time during or after receipt of the study treatment. None of the patients who tested positive for ATAs in this study experienced anaphylaxis or hypersensitivity reactions that were clearly related to ATAs. Many of the patients who tested positive for ATAs in this study continued to receive study treatment (placebo/pertuzumab + trastuzumab + docetaxel), sometimes for prolonged periods after ATAs were first detected. Although 3 patients in the placebo arm and 3 patients in the pertuzumab arm with detectable ATAs experienced hypersensitivity reactions, the investigator assessed the event to be related to docetaxel for 3 patients (2 patients in the placebo arm and 1 patient in the pertuzumab arm) and related to pamidronate in 1 patient (in the placebo arm). The reported course for the events that were reported in the other 2 patients in the pertuzumab arm suggests that the events were simple infusion reactions such as those seen with trastuzumab and other monoclonal antibodies.

Two of 366 patients (0.5%) who were treated with pertuzumab in the Phase I and II studies who had at least one postdose sample available for ATA analysis tested positive for ATAs to pertuzumab. Both patients experienced Grade 3 hypersensitivity reactions that precluded further administration of pertuzumab. A different ATA assay was used in these studies and may contribute to the observed differences between Phase III and Phase I/II studies.

Overall, these data show that anaphylaxis or hypersensitivity reactions as a result of ATAs have occurred in patients who were treated with pertuzumab, although these events were not observed in the pivotal MBC study. Therefore, the detection of ATAs does not necessarily mean that a patient is at a high risk for such reactions or that pertuzumab cannot be continued.

Among the patients with pharmacokinetic (PK) samples that were collected in a substudy of Study WO20698/TOC4129g, only 1 of 20 patients in the pertuzumab arm tested positive for ATAs to pertuzumab. This patient had a slightly lower pertuzumab trough concentration (40.8 μg/mL) when compared with Day 168 data from ATA-negative patients (mean [coefficient of variation %] = 77.8 μg/mL [26.7]). However, the trough concentration was higher than the PK target concentration of 20 μg/mL at all timepoints. Given that only 1 patient tested positive for ATAs to pertuzumab in the PK substudy, a definitive conclusion on whether there is any impact of ATAs on the pharmacokinetics of pertuzumab and on clinical relevance cannot be drawn.

1.2.2.4 Pharmacokinetics of Pertuzumab

Pharmacokinetics in Monotherapy or Combination

The pharmacokinetics of pertuzumab administered as a single agent were studied in two Phase Ia studies with doses ranging from 0.5 to 25.0 mg/kg and in five Phase II studies with a dose of 1050 mg (with no initial loading dose) or an initial loading dose of 840 mg followed by a dose of 420 mg. In all cases, pertuzumab was administered by intravenous (IV) infusion every 3 weeks. Similar PK disposition was observed across

these seven studies and the pharmacokinetics exhibited a biphasic profile that was characterized by a serum clearance of approximately 0.235 L/day, a half-life of approximately 18 days, and a volume of distribution approximating serum volume. No differences in pharmacokinetics have been observed between Caucasian and Asian (mostly Japanese) patients. Pertuzumab exhibited linear pharmacokinetics for doses $\geq$2.0 mg/kg. With an 840-mg initial loading dose followed by 420-mg doses every 3 weeks, serum trough concentrations of pertuzumab were $\geq$20 μg/mL—the target threshold concentration identified in nonclinical xenograft models—in $>$90% of patients.

Five Phase Ib/II studies evaluated the pharmacokinetics of pertuzumab in combination with different anti-cancer agents (capecitabine, erlotinib, gemcitabine, and docetaxel). Four of the five studies had control arms that allowed for a direct assessment of the impact of pertuzumab on the pharmacokinetics of other co-administered anti-cancer agents. Results indicate that pertuzumab does not alter the pharmacokinetics of capecitabine (and its metabolites, including 5-FU), erlotinib, gemcitabine (and its metabolite 2′, 2′ -difluorodeoxyuridine), or docetaxel. In addition, the pharmacokinetics of pertuzumab in combination with other agents were similar to the pharmacokinetics of pertuzumab as a single agent and suggest that there were no changes in pertuzumab pharmacokinetics in the presence of capecitabine, erlotinib, gemcitabine, or docetaxel. The effects of drug-drug interactions (DDIs) between docetaxel, trastuzumab, and pertuzumab were investigated in a substudy of the Phase III Study WO20698/TOC4129g. As expected, because pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other or causing steric hindrance of binding, there was no evidence of a DDI between pertuzumab and trastuzumab (in the presence of docetaxel). Further, there was no evidence of a DDI between pertuzumab and docetaxel (in the presence of trastuzumab).

The potential for a PK DDI of pertuzumab (in combination with trastuzumab) on the pharmacokinetics of carboplatin is currently being studied in a subset of patients in the Phase III Study BIG 4-11/BO25126/TOC4939g.

Population Pharmacokinetic Analysis

A comprehensive population PK analysis was performed with use of data from 481 patients who are enrolled in 12 Phase I, II, and III studies. A two-compartment linear model with first-order elimination from the central compartment describes the pharmacokinetics of pertuzumab across the dose range of 2.0–25.0 mg/kg. In the final model, clearance was 0.235 L/day and central compartment volume was 3.11 L. The median terminal elimination half-life was 18 days.

Lean body weight and serum albumin were identified as statistically-significant covariates for pertuzumab pharmacokinetics. No statistically-significant effects of other covariates on PK parameters were detected, with the inclusion of demographic variables (age, sex, race/ethnicity [Japanese vs. non-Japanese]), laboratory variables related to hepatic and renal function (ALT, AST, total bilirubin, alkaline phosphatase, and

creatinine clearance), and disease variables (Eastern Cooperative Oncology Group [ECOG]/Karnofsky Performance Status, MBC vs. other tumor types, number of metastatic sites, liver metastases, and concomitant chemotherapy). Clearance decreased in patients with higher baseline albumin concentrations and increased in patients with a greater lean body weight. However, sensitivity analyses indicated that a dose adjustment on the basis of these covariates would not lead to a meaningful reduction in PK variability. Further, a sensitivity analysis was conducted to evaluate the impact of baseline body weight on steady-state trough pertuzumab concentrations. The results were then summarized by quartiles of body weight to evaluate the impact of body weight on the achievement of the clinical target concentration (steady-state trough concentration of $\geq$20 μg/mL in 90% of patients). The results indicated that the vast majority of patients (90% or above) remained above the target across all body weight quartiles and supported the validity of the fixed, non–weight-based pertuzumab dosing regimen of an 840-mg initial dose followed by 420-mg doses administered every 3 weeks.

See the Pertuzumab Investigator's Brochure for details on clinical studies.

1.3 BACKGROUND ON TRASTUZUMAB

Trastuzumab is a recombinant humanized anti-p185^{HER2} monoclonal antibody that binds with high affinity to the HER2 protein. In most of the world, trastuzumab is licensed in combination with docetaxel as a first-line treatment for HER2-positive MBC because a significant survival benefit has been demonstrated for the combination compared with chemotherapy alone (Slamon et al. 2001; Marty et al. 2005). On the basis of data from Study BO16348 (Piccart-Gebhart et al. 2005), trastuzumab is registered in the European Union and many other countries for use after adjuvant chemotherapy. In addition, trastuzumab is approved in the European Union as a neoadjuvant therapy. Other data confirm that adjuvant treatment of HER2-positive breast cancer with trastuzumab in combination with chemotherapy is associated with significantly improved outcomes and that the improvement is possibly greater when trastuzumab is integrated with the taxane part of the adjuvant therapy compared with sequential administration (Romond et al. 2005; Perez et al. 2009).

Details on the use of trastuzumab can be found in the Trastuzumab Investigator's Brochure and the Herceptin prescribing information.

1.3.1 Trastuzumab Safety Data

Details of the adverse events associated with the clinical use of trastuzumab can be found in the Trastuzumab Investigator's Brochure. To minimize the risk of cardiac dysfunction, only patients who have adequate cardiac function (LVEF $\geq$55%) will be enrolled in the study. Patients with particular cardiac risk factors will be excluded.

1.3.2 Pharmacokinetics of Trastuzumab

Analyses in clinical studies showed that trastuzumab has dose-dependent, non-linear pharmacokinetics with dose-dependent clearance and half-life. The volume of distribution approximates the serum volume. At therapeutic doses, the half-life is approximately 26–38 days and may persist in the circulatory system for up to 27 weeks after the end of treatment.

Refer to the Trastuzumab Investigator's Brochure for further information.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Pertuzumab has shown activity and a favorable benefit-risk profile in patients whose disease progressed after prior HER2-directed therapies for metastatic disease. Data from Study WO20697 confirm that both trastuzumab and pertuzumab are active against HER2-positive breast cancer when administered with docetaxel and that the two antibodies administered together are more active than either one alone when administered with docetaxel. In addition, pertuzumab appears to have a favorable benefit-risk profile in patients who have not received prior chemotherapy for metastatic disease with inclusion of patients who had previously received trastuzumab in the adjuvant setting. The safety profile of pertuzumab appears to be acceptable in the metastatic setting and is currently under evaluation for HER2-positive EBC. In the curative treatment setting, certain acute adverse events or potential chronic organ effects (e.g., cardiac) may constitute a specific concern for pertuzumab. In studies that have been conducted to date, there does not appear to be an increased risk for cardiac adverse events with pertuzumab compared with other HER2-directed therapies. Although initial safety data to date with pertuzumab in previously-untreated patients in the neoadjuvant (Gianni et al. 2012) and metastatic settings (Baselga et al. 2012a) appear acceptable, *the* safety monitoring plan for this study includ*es* appropriate eligibility criteria, dose modification guidelines, and regular monitoring of accumulating patient safety data by *the Sponsor's study team and* has been put in place to minimize any potential risk in the study patient population.

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 trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel as neoadjuvant treatment prior to surgery in patients who are chemotherapy-naive with early-stage or locally advanced HER2–positive breast cancer as measured by tpCR rate assessed by an Independent Review Committee (IRC).

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel as neoadjuvant treatment prior to surgery in patients with early-stage or locally advanced HER2-positive breast cancer as measured by the following:

- tpCR rate assessed by the local pathologist
- bpCR rate assessed by the IRC
- bpCR rate assessed by the local pathologist
- Clinical response rates during Cycles 1–4 in accordance with Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (see Appendix 4)
- Event-free survival (EFS)
- DFS
- Overall survival

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of each treatment regimen

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore relationships between findings from the sentinel lymph node (SLN) biopsy tissue sample (if biopsy is performed) and the axillary lymph node dissection tissue sample (ALND) obtained during the surgery that is undertaken after neoadjuvant treatment
- To characterize the pharmacokinetics of pertuzumab after IV infusion in a subset of Chinese patients with early-stage or locally advanced HER2-positive breast cancer
- To analyze biomarkers in tumor tissue *taken at baseline or at the time of resection* (*markers analyzed may include but are not limited to* HER2/3 mRNA and/or protein, PIK*3CA*, phosphatase and tensin homolog [PTEN], *programmed death–ligand 1 [PD-L1], and cluster of differentiation 8 [CD8]), and serum (e.g.,* HER ligands *and* HER2 ECD) and evaluate correlations with clinical outcomes and, if applicable, safety outcomes
- To analyze the effect of HER2 ECD on pharmacokinetics of pertuzumab
- To analyze the effect of ATAs on pharmacokinetics, safety, and efficacy
- To assess tpCR in relation to clinical response rate, EFS, DFS, and overall survival

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is an Asia-Pacific regional, randomized, double-blind, Phase III, multicenter study to evaluate treatment with trastuzumab + pertuzumab + docetaxel compared with trastuzumab + placebo + docetaxel in patients who are chemotherapy-naive with early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0) HER2-positive breast cancer. A primary tumor with the longest diameter of > 2 cm is required.

Patients will be randomized in a 2:1 ratio to Arm A or Arm B, respectively, and treated every 3 weeks for four cycles prior to surgery as follows:

- Arm A

  Trastuzumab (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for Cycles 2–4)

  Pertuzumab (840-mg loading dose for Cycle 1, followed by 420 mg for Cycles 2–4)

  Docetaxel (75 mg/m^2 for Cycles 1–4)
- Arm B

  Trastuzumab (8-mg/kg loading dose for Cycle 1, followed by 6 mg/kg for Cycles 2–4)

  Placebo (Cycles 1–4)

  Docetaxel (75 mg/m^2 for Cycles 1–4)

Approximately 328 eligible patients will be enrolled at approximately 24 sites, resulting in approximately 219 patients in Arm A and 109 patients in Arm B. Randomization will be stratified by disease category (early-stage or locally advanced) and hormone-receptor status (positive for estrogen receptor [ER] and/or progesterone receptor [PgR] or negative for both).

After completing four cycles of neoadjuvant treatment, all patients who are eligible for surgery will undergo surgery and have their pathologic response evaluated. After surgery, patients will receive 500–600 mg/m^2 5-FU, 90–120 mg/m^2 epirubicin, and 500–600 mg/m^2 FEC every 3 weeks for three cycles (Cycles 5–7). Patients will then continue HER2-targeted therapy in accordance with the initial randomization every 3 weeks until disease recurrence (as assessed by the investigator) or unacceptable toxicity for up to 1 year total (17 cycles with inclusion of four cycles in the neoadjuvant setting) as follows:

- Arm A

  Trastuzumab (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9–20)

  Pertuzumab (840-mg loading dose for Cycle 8, followed by 420 mg for Cycles 9–20)

- Arm B

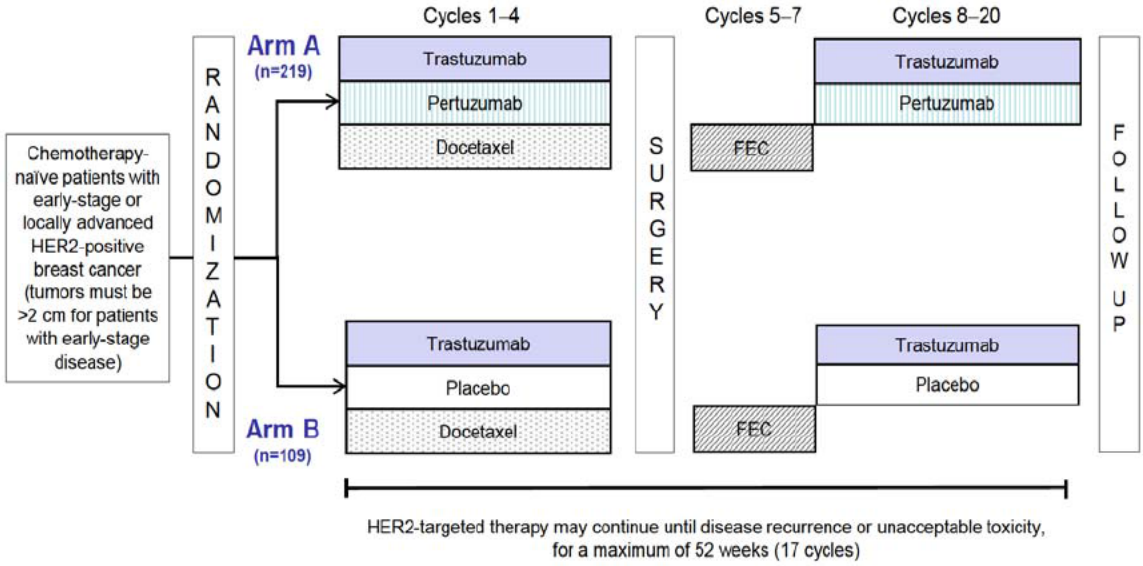
  Trastuzumab (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9–20)

  Placebo (Cycles 8–20)

For patients with tumors that are ER and/or PgR positive, hormonal agents (tamoxifen or an aromatase inhibitor for postmenopausal patients or tamoxifen, with or without *ovarian suppression, or aromatase inhibitor with* ovarian suppression for premenopausal patients) should be started at the end of FEC chemotherapy and given for at least 5 years. Radiotherapy is to be given as clinically indicated at the end of FEC chemotherapy.

The study design is displayed graphically in Figure 1.

Figure 1 Study Schema



FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; HER = human epidermal growth factor receptor.
Note: Patients will be followed for disease recurrence and survival or until 5 years after randomization of the last patient.

Patients who discontinue neoadjuvant (preoperative) HER2-targeted therapy as a result of toxicity and patients who are not eligible for surgery will be managed as per local practice. Patients who discontinue adjuvant (postoperative) chemotherapy as a result of chemotherapy-related toxicity will continue with HER2-targeted therapy until they have received a total of 17 cycles of treatment. Approximately 28 days after the last dose of study treatment, a final safety assessment will be performed before a patient enters

long-term safety follow-up. Patients will be followed for disease recurrence and survival or until 5 years after randomization of the last patient.

Patients will be evaluated for clinical response prior to surgery (i.e., during Cycles 1–4) in accordance with RECIST v1.1. Patients will be evaluated for pathologic response after surgery and evaluated for disease recurrence. The primary efficacy objective will be evaluated when all patients *who are eligible for surgery* have completed the*ir surgical* treatment *with the assessment of pathological response*. Patients will be evaluated for safety throughout the study with laboratory tests and adverse event reports. Serum samples will be collected from a subset of approximately 50 Chinese patients for characterization of pertuzumab pharmacokinetics.

A schedule of activities is provided in Appendix 1.

3.1.2 Independent Review Committee

An IRC that consists of independent experts who are not involved in the study (including approximately *three* pathologists) will evaluate the pathologic response.

Details of the composition, roles, and responsibilities of the IRC will be provided in a separate charter.

The IRC will remain blinded to the treatment assignment for the formal efficacy analyses. The Sponsor will remain blinded to the IRC assessments.

3.1.3 Safety *Data Review*

The Sponsor's study team will review adverse events*, serious adverse events, and any other safety data* in the study on a regularly scheduled basis.

It is the responsibility of the *study team* to review accumulating safety data, assess and monitor *ongoing* safety of patients, evaluate potential changes to the clinical study protocol, and ultimately safeguard patient safety.

3.2 END OF STUDY

The study will formally end approximately 5 years after the date of randomization of the last patient.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Combining Pertuzumab, Trastuzumab, and Docetaxel

The combination of pertuzumab and trastuzumab is scientifically compelling based on their complementary modes of action and on the nonclinical data as previously described. There is clinical evidence that the combination is both active and well tolerated in carefully selected patients (Walshe et al. 2006; Baselga et al. 2007). These data are consistent with other data on the use of combined biological agents, which

suggest that such combinations are highly active and associated with encouraging tolerability (Pegram et al. 2005). The magnitude of clinical benefit and the acceptable safety profile in this study confirm the positive benefit-risk ratio of pertuzumab combined with trastuzumab and docetaxel in patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer, including patients from Asia (Baselga et al. 2012a). This level of clinical benefit has exceeded expectation (see Section 1.2.2.1). Docetaxel is an established agent in the therapy of breast cancer and registered for use in this indication.

3.3.2 Rationale for Neoadjuvant Therapy

Adjuvant systemic therapies for breast cancer (i.e., drugs to reduce the risk of breast cancer recurrence) historically have been administered after definitive breast surgery. Preoperative or neoadjuvant systemic chemotherapy that was once reserved for patients with locally advanced breast cancer *for* whom the goal was to render large breast cancers operable has become increasingly common. There are several potential rationales for neoadjuvant treatment for early-stage breast cancer. Giving preoperative chemotherapy permits breast conservation in some patients who would otherwise require mastectomy and may improve cosmesis in existing candidates for breast conservation (Fisher et al. 2002; Alm El-Din and Taghian 2009). Preoperative therapy also enables the oncologist to evaluate tumor response and discontinue ineffective therapy or substitute an alternative systemic therapy. Further, a patient's response to neoadjuvant chemotherapy may provide prognostic information that can supplement conventional prognostic data such as initial staging, tumor grade, and receptor status. Finally, the neoadjuvant setting provides investigators with the unique opportunity to examine modulation of *tumor* tissue biomarkers from the time of biopsy to the time of definitive breast surgery after completion of preoperative systemic therapy *in patients who have residual disease*.

A meta-analysis of approximately 4000 patients who are enrolled in nine studies of neoadjuvant versus adjuvant chemotherapy or endocrine therapy found no evidence that sequencing of systemic therapy and surgery alters distant disease recurrence or overall survival (Mauri et al. 2005). Of note, patients who received neoadjuvant therapy compared with those who received postoperative adjuvant therapy had an increased risk of locoregional recurrence, which has been attributed to the omission of definitive local therapy in some of the neoadjuvant studies (Mauri et al. 2005). Under the assumption that definitive local therapy will be provided, preoperative systemic therapy appears to be an acceptable alternative to standard postoperative systemic therapy in patients with early-stage breast cancer and facilitating the development of new drugs for use in the neoadjuvant setting is a worthwhile objective.

At the completion of the neoadjuvant therapy, patients will undergo surgery. The surgical specimen will be reviewed and the pathologic response to therapy evaluated. The desired outcome of the neoadjuvant therapy is pCR. There is evidence that those

patients who achieve a pCR have survival advantage (Fisher et al. 1998; Kurosumi 2004; Bear et al. 2006; Kaufmann et al. 2006). The pCR rate is therefore deemed to be a suitable primary endpoint in a study on neoadjuvant therapy.

3.3.3 Rationale for Adjuvant Therapy

The combination of pertuzumab and trastuzumab as an adjuvant therapy is scientifically compelling based on their complementary mechanisms of action and the available nonclinical data as described in Section 1.2.1. This rationale is supported by the clinical data from Studies WO20697, BO17929, and WO20698/TOC4129g (Gelmon et al. 2008; Baselga et al. 2009; 2012a).

After surgery, patients will receive adjuvant chemotherapy in the form of standard FEC combination therapy. Anthracyclines (generally used in combination with 5-FU and cyclophosphamide) have a central role in the management of breast cancer (Romond et al. 2005; Poole et al. 2006). Specifically, there might be a particular activity associated with the use of anthracyclines in patients whose tumors overexpress chromosome 17 because polysomy 17 is associated with overexpression of HER2, topoisomerase II (topoisomerase II being the target for anthracyclines), and other potentially relevant proteins such as p53 (Bartlett et al. 2008; Gennari et al. 2008). There is evidence that the combination of cardiotoxic anthracyclines (such as epirubicin) with trastuzumab may be associated with acceptable cardiac tolerability in patients who are selected for their good cardiac function (Untch et al. 2004; Buzdar et al. 2005). It is possible that pertuzumab will be equally tolerable when given in combination with anthracyclines to similarly selected patients. However, in the interest of patient safety, *adjuvant* FEC treatment will be separated from *neoadjuvant* pertuzumab treatment by a minimum of 5 weeks.

The clinical data that pertain to pertuzumab suggest it has a promising benefit-risk profile and could be a suitable additional agent for use in early, potentially curable, breast cancer.

3.3.4 Rationale for Docetaxel Dosage

Docetaxel at a dose of 100 mg/m^2 given every 3 weeks in combination with trastuzumab has been associated with a positive benefit-risk ratio compared with docetaxel alone in patients with HER2-overexpressing MBC (Marty et al. 2005). However, based on the results from a Phase Ib study (Study BO17021), the maximum tolerated dose of docetaxel in combination with pertuzumab is 75 mg/m^2. The benefits and risks associated with different docetaxel doses (single agent) have been established in a randomized study that suggests that all three doses of docetaxel (60, 75, and 100 mg/m^2) were active with manageable toxicity. Depending on the goals of therapy and the individual characteristics of the patient, each of the three doses may be appropriate, with lower doses having potential utility in patients who are frail or have specific tolerability concerns (Harvey et al. 2006). The rate of febrile neutropenia in Asian patients was

notably higher than that in the other populations where docetaxel was administered at 75 mg/m^2 and could be escalated to 100 mg/m^2 if well tolerated (Study WO20698/TOC4129g). This is consistent with general observations on the tolerability of taxanes in such populations (Fujiwara et al. 1999; Sato et al. 2006) and with the fact that docetaxel is registered at lower doses in Asian countries than in Western countries. To increase the tolerability of the combined regimen, the dose of docetaxel used in this study will be 75 mg/m^2.

3.3.5 Rationale for Trastuzumab and Pertuzumab Dosages

Based on the PK data, lack of DDI between trastuzumab and pertuzumab and positive clinical data, a pertuzumab loading dose of 840 mg followed by a 420-mg maintenance dose every 3 weeks was determined for pertuzumab (see Section 1.2.2.4).
A trastuzumab loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks is deemed appropriate on the basis of trastuzumab pharmacokinetics (see Section 1.3.2).

3.3.6 Rationale for Biomarker Assessments

The exploratory biomarker analyses in this study will be used to assess the potential prognostic and/or predictive value of candidate markers or biomarker panels, improve diagnostic tests, improve understanding of breast cancer biology, or discover new biomarker profiles that are related to treatment benefit, treatment safety, and/or disease characteristics. The collection of samples for exploratory biomarker research is mandatory.

Biomarkers to be considered for exploratory analyses are:

- Molecules involved in downstream signaling of HER2
- Molecules that belong to a group of related receptor tyrosine kinases that could serve as salvage routes for an inhibited HER2 pathway
- Ligands of HER family proteins that induce activation of the HER pathway

Such molecules that are considered for analyses may include but are not limited to PTEN, PIK3CA mutations, HER3 and HER2 mRNA, *PD-L1, CD8,* and *other markers that are relevant to breast cancer*.

If appropriate, a refinement of the translational research plan *may* be implemented prior to the data cutoff date to take into account emerging data in the literature and allow for the latest state-of-the-art technology to be applied.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is tpCR, defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes after completion of neoadjuvant therapy and

surgery (i.e., ypT0/is, ypN0 in accordance with the current AJCC staging system) as assessed by the IRC (see Appendix 8).

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- tpCR assessed by a local pathologist
- bpCR defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen after completion of neoadjuvant therapy and surgery (i.e., ypT0/is in accordance with the current AJCC staging system) as assessed by the IRC
- bpCR assessed by a local pathologist
- Clinical response during Cycles 1–4 in accordance with RECIST v1.1
- EFS defined as time from randomization to the first documentation of one of the following events:

    Disease progression (before surgery) as determined by the investigator with use of RECIST v1.1

        Any evidence of in situ contralateral disease will not be identified as progressive disease (PD)

        Any evidence of invasive contralateral disease will be considered disease progression

    Disease recurrence (local, regional, distant, or contralateral) after surgery

    Death from any cause
- DFS defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of one of the following events:

    Disease recurrence (local, regional, distant, or contralateral) after surgery

    Death from any cause
- Overall survival defined as the time from randomization to death from any cause

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events and serious adverse events
- Incidence of symptomatic LVSD (heart failure) defined as the occurrence of symptomatic LVEF decrease or definite or probable cardiac death
- Incidence of asymptomatic decrease in LVEF defined as an absolute decrease of ≥ 10 percentage points from baseline to an LVEF of $< 50\%$
- LVEF values over the course of the study
- Laboratory test result abnormalities

3.4.3 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- To explore relationships between pathology findings from the SLN biopsy tissue sample, if the biopsy is performed, and the ALND tissue sampled obtained during the surgery undertaken after neoadjuvant treatment
- Observed pertuzumab concentrations at all specified PK sampling timepoints
- Observed pertuzumab concentrations compared with concentrations in Caucasian patients with HER2-positive breast cancer from other studies
- Observed pertuzumab concentrations during neoadjuvant treatment compared with concentrations during adjuvant treatment (postoperative)
- Expression levels or incidence of biomarkers at baseline and *in resection specimen tissue*, *especially* for patients with residual disease, at the time of surgery (i.e., after neoadjuvant treatment) and their relationship to efficacy or safety parameters
- To analyze the effect of HER2 ECD on pharmacokinetics of pertuzumab
- Incidence of ATAs and relationship with PK, safety, and efficacy outcome measures
- tpCR in relation to clinical response, EFS, DFS, and overall survival

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 328 patients who are chemotherapy-naive with early-stage or locally advanced HER2-positive breast cancer will be enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- Breast cancer that meets the following criteria:

  Histologically confirmed invasive breast carcinoma with a primary tumor size of $>$ 2 cm by standard local assessment technique

  Stage at presentation: early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0)
- HER2-positive breast cancer confirmed by a Sponsor-designated central laboratory and defined as 3+ score by IHC in $>$ 10% of immunoreactive cells or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals $\geq$ 2.0) by in situ hybridization (ISH)

  A tumor sample that consists of a tumor block or eight unstained, freshly cut slides must be available for central laboratory HER2 testing by IHC and ISH. Note that up to *an* additional *seven* slides are required for exploratory biomarker research. *Therefore, 15 slides are requested at screening.*

- Known hormone receptor status (ER and PgR)
- ECOG Performance Status ≤1 (see Appendix 5)
- Completion of all necessary baseline laboratory and radiologic investigations prior to randomization
- Baseline LVEF ≥55% measured by echocardiography (ECHO; preferred) or multiple-gated acquisition (MUGA) scan
- For women who are not postmenopausal (≥12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use one highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception during the treatment period and for at least 7 months after the last dose of study treatment (see Section 5.1.3)
- For men: agreement to use reliable and effective contraceptive measures during the treatment period and for at least 7 months after the last dose of study treatment (see Section 5.1.3)
- 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:

- Stage IV (metastatic) breast cancer
- Inflammatory breast cancer
- Previous anti-cancer therapy or radiotherapy for any malignancy
- History of other malignancy *within 5 years prior to screening*, except for *appropriately-treated* carcinoma in situ of the cervix*, non-melanoma skin* carcinoma*, or Stage I uterine cancer*
- Concurrent anti-cancer treatment in another investigational study, including hormone therapy, bisphosphonate therapy, or immunotherapy
- Major surgical procedure that is unrelated to breast cancer within 4 weeks prior to randomization or from which the patient has not fully recovered
- Serious cardiac illness or medical condition including but not limited to the following:

  History of documented heart failure or systolic dysfunction (LVEF <50%)

  High-risk uncontrolled arrhythmia, such as atrial tachycardia with a heart rate >100 bpm at rest, significant ventricular arrhythmia (e.g., ventricular tachycardia), or higher-grade atrioventricular (AV) block (i.e., Mobitz II second-degree AV block or third-degree AV block)

  Angina pectoris that requires anti-angina medication

  Clinically-significant valvular heart disease

  Evidence of transmural infarction on ECG

  Poorly-controlled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg)

- Other concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness
- Any of the following abnormal laboratory test results immediately prior to randomization:

  Total bilirubin $> 1.5 \times$ upper limit of normal (ULN) or, for cases of known Gilbert's syndrome, total bilirubin $> 2 \times$ ULN

  AST and/or ALT $> 1.25 \times$ ULN

  Alkaline phosphatase $> 2.5 \times$ ULN

  Serum creatinine $> 1.5 \times$ ULN

  Total WBC count < 2500 cells/μL

  Absolute neutrophil count < 1500 cells/μL

  Platelet count $< 100{,}000$ cells/μL
- Sensitivity to any of the study medications, any of the ingredients or excipients of these medications, or benzyl alcohol
- Pregnant or lactating

  A negative serum pregnancy test result is required for all women who are not postmenopausal (≥ 12 months of amenorrhea).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient randomization number and treatment assignment from the interactive voice/Web–based response system (IxRS). Patients should receive their first dose of study treatment on the day of randomization, if possible, but no later than 5 business days after randomization. Patients will be randomized in a 2:1 ratio to one of the two treatment arms (pertuzumab or placebo) with use of the IxRS. Patients will be enrolled with a permuted block randomization procedure that uses the following stratification factors:

- Disease category: early-stage (T2-3, N0-1, M0) or locally advanced (T2-3, N2 or N3, M0; T4, any N, M0)
- Hormone-receptor status: positive for ER and/or PgR; negative for both

The investigator and the patient will be blinded to the treatment assignment. All other individuals who are directly involved in this study will remain blinded to the treatment assignment until completion of the primary analysis. Patient *treatment assignment* will not be unblinded until after the final 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 treatment unblinding is necessary for patient management (in the case of a serious adverse event), the investigator will be able to break the treatment code by contacting 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 treatment unblinding (e.g., accidental treatment unblinding, treatment unblinding as a result of a serious adverse event).

Although PK and HER2 ECD samples must also be obtained from patients who are randomized to the placebo arm to maintain the blinding to the treatment assignment, only the PK and HER2 ECD samples from patients who are treated with pertuzumab and enrolled in the PK substudy in China will be tested. The study personnel that are responsible to perform the PK and HER2 ECD assays will be unblinded to a patient's treatment assignment to identify the appropriate PK and HER2 ECD samples to be analyzed.

As per health authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (see Section 5.7) considered by the investigator to be related to study drug.

4.3 STUDY TREATMENT

Eligible patients will be treated with trastuzumab, pertuzumab, and docetaxel (Arm A) or trastuzumab, placebo, and docetaxel (Arm B) for four cycles in the neoadjuvant setting. After surgery, patients will receive three cycles of FEC chemotherapy. Patients will then continue HER2-targeted therapy that consists of trastuzumab and pertuzumab (Arm A) or trastuzumab and placebo (Arm B) until disease recurrence as assessed by the investigator or unacceptable toxicity for up to 1 year in total (17 cycles, including four cycles in the neoadjuvant setting).

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Trastuzumab

Trastuzumab (lyophilized formulation) for use in this study will be supplied by the Sponsor as a freeze-dried preparation. All trastuzumab is supplied for IV administration. Trastuzumab is formulated in histidine, trehalose, and polysorbate 20. Vials of trastuzumab are shipped with cool packs at a temperature range of 2°C–8°C (36°F–46°F) and must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. Do not use beyond the expiration date stamped on the vial. DO NOT FREEZE.

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

should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted trastuzumab may result in problems with the amount of trastuzumab that can be withdrawn from the vial.

The Sponsor will provide trastuzumab to all study sites labeled for investigational use only.

For further details, see the Trastuzumab Investigator's Brochure as well as local prescribing information for trastuzumab.

4.3.1.2 Pertuzumab and Placebo

Pertuzumab is provided as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine-acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-mL vial (14 mL solution per vial) contains approximately 420 mg of pertuzumab. Pertuzumab-matching placebo has the identical formulation but does not contain the antibody.

Upon receipt of pertuzumab, vials are to be refrigerated at 2°C–8°C (36°F–46°F) until use. Pertuzumab vials should not be used beyond the expiration date provided by the manufacturer. Because the formulation does not contain a preservative, the vial seal may only be punctured once. Any remaining solution should be discarded. Vial contents should be protected from light and should not be frozen. The solution of pertuzumab for infusion, diluted in polyvinyl chloride (PVC) or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection, USP, may be stored for up to 24 hours prior to use. Diluted pertuzumab has been shown to be stable for up to 24 hours at a temperature range of 2°C–25°C (36°F–46°F). However, since diluted pertuzumab contains no preservative, the diluted solution should be stored refrigerated at 2°C–8°C (36°F–46°F).

The Sponsor will provide pertuzumab and placebo to all study sites labeled for investigational use only. Pertuzumab and placebo will be labeled in accordance with the regulatory requirements of each country in which this study is being conducted as well as the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice.

For further details, see the Pertuzumab Investigator’s Brochure.

4.3.1.3 Docetaxel

Where permitted by regulatory requirements, sites will obtain and utilize commercially available docetaxel. For details on the docetaxel formulation, see the local prescribing information for docetaxel.

4.3.1.4 FEC Chemotherapy

For details on the FEC chemotherapy formulations, see the local prescribing information for 5-FU, epirubicin, and cyclophosphamide.

4.3.2 Dosage, Administration, and Compliance

Study treatment will be administered in 3-week (21[±3] days) cycles (with the assumption that there is no delay as a result of an adverse event). Patients will complete four cycles of neoadjuvant treatment prior to surgery with treatments administered to the two arms in the following order:

- Arm A: trastuzumab, pertuzumab, and docetaxel
- Arm B: trastuzumab, placebo, and docetaxel

After surgery, patients will receive three cycles of FEC chemotherapy (Cycles 5–7). Patients will then continue HER2-targeted therapy every 3 weeks until disease recurrence as assessed by the investigator or unacceptable toxicity for up to 1 year total (17 cycles, including four cycles in the neoadjuvant setting) with treatments administered to the two arms in the following order:

- Arm A: trastuzumab and pertuzumab
- Arm B: trastuzumab and placebo

Further details on dosing, administration, and compliance are provided below.

4.3.2.1 Trastuzumab

Trastuzumab will be administered by IV infusion on Day 1 of each specified 3-week cycle, as outlined below.

- Neoadjuvant treatment (prior to surgery)

  Patients in Arms A and B will receive trastuzumab at a loading dose of 8 mg/kg for Cycle 1 and a dose of 6 mg/kg for Cycles 2–4. The initial dose of trastuzumab will be administered over 90 (±10) minutes, and patients will be observed for 30 minutes after the infusion. If the infusion is well tolerated, subsequent doses may be administered over 30 (±10) minutes and patients will be observed for 30 minutes after the infusion.

- Adjuvant treatment (after surgery and three cycles of FEC chemotherapy [Cycles 5–7])

  Patients in Arms A and B will receive trastuzumab at a reloading dose of 8 mg/kg for Cycle 8 and a dose of 6 mg/kg for Cycles 9–20. If infusions are well tolerated during the neoadjuvant treatment period, subsequent infusions may be administered over 30 (±10) minutes and patients will be observed for 30 minutes after the infusion.

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 pertuzumab is administered. 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 discontinue treatment.

The amount of trastuzumab administered is calculated in accordance with the patient's actual body weight with no upper limit. Weight should be recorded at baseline and at every scheduled visit. The amount to be administered must be recalculated if the patient's body 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 the trastuzumab dose in subsequent cycles.

Dosage modifications are not permitted (except as required because of changes in body weight). Treatment interruption or discontinuation is permitted for toxicity, including cardiotoxicity (see Sections 5.1.1 and 5.1.2). If trastuzumab must be delayed for a day or more, all study treatments should be delayed for the same time frame. If trastuzumab is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment.

If a patient misses a dose of trastuzumab for any cycle and the time between doses is ≥ 6 weeks, the patient should receive a reloading dose of 8 mg/kg of trastuzumab. Subsequent trastuzumab doses of 6 mg/kg will continue to be administered every 3 weeks, beginning 3 weeks after the loading dose.

4.3.2.2 Pertuzumab and Placebo

Pertuzumab or matching placebo will be administered by IV infusion on Day 1 of each specified 3-week cycle after the trastuzumab infusion observation period as outlined below. Study site staff and the patient will be blinded as to whether pertuzumab or matching placebo is administered.

- Neoadjuvant treatment (prior to surgery)

  Patients will receive pertuzumab or placebo at a loading dose of 840 mg for Cycle 1 and a dose of 420 mg for Cycles 2–4. The initial dose of pertuzumab or placebo will be administered over 60 (± 10) minutes, and patients will be observed for 60 minutes after the infusion. If the infusion is well tolerated, subsequent doses may be administered over 30 (± 10) minutes and patients will be observed for 30 minutes after the infusion.

- Adjuvant treatment (after surgery and three cycles of FEC chemotherapy [Cycles 5–7])

  Patients will receive pertuzumab or placebo at a reloading dose of 840 mg for Cycle 8 and a dose of 420 mg for Cycles 9–20. If infusions are well tolerated during the neoadjuvant treatment period, subsequent infusions may be administered over 30 (± 10) minutes and patients will be observed for 30 minutes after the infusion.

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 discontinue treatment.

Dosage modifications are not permitted. Treatment interruption or discontinuation is permitted for toxicity, including cardiotoxicity (see Sections 5.1.1 and 5.1.2). If the administration of pertuzumab or placebo must be delayed for a day or more, all study treatments should be delayed for the same time frame. If the treatment with pertuzumab or placebo is withheld for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment.

If a patient in Arm A misses a dose of pertuzumab for any cycle and the time between doses is ≥6 weeks, the patient should receive a reloading dose of 840 mg of pertuzumab. Subsequent pertuzumab doses of 420 mg will continue to be administered every 3 weeks, beginning 3 weeks after the loading dose.

4.3.2.3 Docetaxel

Patients in Arms A and B will receive docetaxel at a dose of 75 mg/m^2 every 3 weeks for four cycles (Cycles 1–4). Docetaxel will be administered by IV infusion on Day 1 of each cycle after the pertuzumab infusion observation period. Patients will be observed closely from the start of the infusion for hypersensitivity reactions, which may occur within minutes. Severe hypotension, bronchospasm, or generalized rash/erythema requires immediate discontinuation of docetaxel and appropriate treatment. The infusion may be slowed for minor symptoms such as flushing or local cutaneous reactions. Patients who experience severe hypersensitivity reactions should not continue in the study. Premedication that consists of an oral corticosteroid such as dexamethasone 16 mg/day (may be divided into two 8-mg doses per day) on Day −1, Day 1, and Day 2 may be administered if not contraindicated. Similarly, prophylactic granulocyte colony-stimulating factor (G-CSF) may be used to mitigate the risk of hematological toxicities.

The amount of docetaxel that is administered is calculated in accordance with the patient's body surface area. 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. The amount to be administered must be recalculated if the patient's body 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 *is* provided*, which may be used* for the determination of body surface area (see Appendix 7).

Guidelines for docetaxel dosage modification and treatment interruption or discontinuation as a result of toxicity are provided in Section 5.1.2. If docetaxel must be delayed for a day or more, all study treatments should be delayed for the same time frame. If docetaxel is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment.

4.3.2.4 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy

After surgery, patients in Arms A and B will receive FEC chemotherapy every 3 weeks for three cycles (Cycles 5–7). The administration of therapy in Cycle 5 should not occur until 2 weeks after surgery.

The amount of each chemotherapy agent that is administered is calculated in accordance with the patient's body surface area. Weight and height should be recorded at baseline and weight should be recorded at every scheduled visit. The amount to be administered must be recalculated if the patient's body 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 be used as the new baseline to calculate the dose in subsequent cycles. A nomogram *is* provided*, which may be used* for the determination of body surface area (see Appendix 7).

Dosage modification and treatment interruption or discontinuation are permitted for FEC chemotherapy as indicated in the relevant local label for each agent and will be managed in accordance with local practice.

5-Fluorouracil

5-FU will be administered at 500–600 mg/m^2 on Day 1 of Cycles 5–7. It may be given as an IV bolus or IV infusion in accordance with local policy. Patients with a body surface area of >2 m^2 should receive a dose of 1200 mg.

Epirubicin

Epirubicin will be administered at 90–120 mg/m^2 on Day 1 of Cycles 5–7. It may be given as an IV bolus or IV infusion in accordance with local policy.

Cyclophosphamide

Cyclophosphamide will be administered at 500–600 mg/m^2 on Day 1 of Cycles 5–7. It may be given as an IV bolus or IV infusion in accordance with local policy. Patients with a body surface area of >2 m^2 should receive a dose of 1200 mg.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) that are required for completion of this study (trastuzumab, pertuzumab, and placebo) will be provided by the Sponsor. Depending on local legislation, docetaxel may also be considered an IMP in this study. Where permitted by regulatory requirements, sites will obtain and utilize commercially available docetaxel. The study site will acknowledge receipt of IMPs with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site in accordance with 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-Study Access to Pertuzumab

The Sponsor does not intend to provide pertuzumab or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

Patients who experience disease progression before the end of neoadjuvant therapy will be withdrawn from study treatment and treated as clinically indicated in accordance with local practice. Patients who complete chemotherapy and surgery but then relapse (either during or after completion of adjuvant pertuzumab and trastuzumab) will be treated as clinically indicated and relevant follow-up information about subsequent therapies and outcomes will be collected.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) or therapy used by a patient at any time from 7 days prior to randomization to the treatment completion or discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Any non–protocol-required therapeutic or surgical procedure that occurs during the study period is also considered a concomitant therapy and must be recorded. Information with regard to concomitant medications and treatments should include the date, reason, description of the medication, treatment or procedure, and any associated clinical findings. Special attention should be paid to reporting any medications associated with the treatment of a suspected or confirmed cardiac event, including an asymptomatic decrease in LVEF.

4.4.1 Surgery

Patients in both cohorts are scheduled to undergo surgery after four cycles of neoadjuvant therapy. Patients may undergo breast-conserving surgery or mastectomy in accordance with routine clinical practice.

Before the initiation of neoadjuvant treatment, the primary tumor site *must* be physically marked per the standard local practice (e.g., skin tattoo or surgical clip) to enable appropriate surgical excision in case of tumor regression during neoadjuvant therapy.

In the event that a biopsy of the sentinel lymph node (SLNB) is performed, it is recommended that both dye and isotope be used. The dye and isotope should not be injected into the tumor itself because they may alter the tissue and affect the molecular analyses to be performed on the tumor tissue sample.

Ongoing clinical studies are evaluating the value of SLNB tissue sample and the role of axillary radiotherapy as an alternative to axillary dissection and identifying subgroups of patients who may be able to omit axillary dissection after a positive SLNB test result. Investigators may follow the local common practice or guidelines based on emerging data once they have been incorporated into institutional, local, national, or international guidelines (e.g., National Comprehensive Cancer Network, European Society for Medical Oncology, St. Gallen, or Lisbon Conference).

4.4.2 Permitted Therapy

In general, all medications that are taken by the patient for concomitant diseases should continue during the study treatment period. Any medication that is necessary for the supportive management of the patient may be used at the discretion of the investigator.

Acceptable methods of contraception must be used when the patient is not surgically sterilized or does not meet the study definition of postmenopausal (see Section 5.1.3).

The following treatments are permitted during the study:

- For patients with tumors that are ER and/or PgR positive: hormonal agents (tamoxifen or an aromatase inhibitor for postmenopausal patients; tamoxifen with or without *ovarian suppression, or aromatase inhibitor with* ovarian suppression for premenopausal patients) initiated at the end of FEC chemotherapy and administered for at least 5 years
- Radiotherapy (administered as clinically indicated at the end of FEC chemotherapy and in accordance with local standard practice)
- H_1- and H_2-receptor antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics for treatment of arterial hypertension with a goal of reducing blood pressure to $<$140/90 mmHg;

β-blockers, calcium channel blockers, and digoxin for heart rate control; thrombocyte aggregation inhibitors

- Analgesics/anti-inflammatories (e.g., paracetamol/acetaminophen, meperidine, and opioids)
- Short-term use of corticosteroids to treat or prevent allergic or infusion reactions
- Anti-emetic *treatments* (e.g., approved prophylactic serotonin-antagonists *and* benzodiazepines)
- Medication to treat diarrhea (e.g., loperamide)
- Colony-stimulating factors (e.g., G-CSF)
- Vitamin and mineral supplements
- Bisphosphonates (used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines)
- Prophylaxis against hepatitis B reactivation (e.g., lamivudine)

All concomitant medications are to be reported through the treatment completion or discontinuation visit. Thereafter, only medications and therapies that are applicable for long-term reporting must be reported including the following:

- Breast cancer treatments (e.g., hormone therapy)
- Anti-cancer treatments for recurrence
- Bisphosphonate or denosumab therapy
- Medications related to the treatment of serious adverse events that are applicable for long-term reporting

4.4.3 Prohibited Therapy

Use of the following therapies is prohibited during the treatment period of the study:

- Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy), immunotherapy, and biological anti-cancer therapy
- Any targeted anti-cancer therapy (e.g., lapatinib, neratinib)
- High doses of systemic corticosteroids, defined as $>$20 mg of dexamethasone a day (or equivalent) for $>$7 consecutive days
- Any investigational agent except for those used for this study
- Herbal remedies initiated *for cancer treatment*

  *Other h*erbal remedies are *discouraged but* permitted and must be reported on the appropriate eCRF.
- Any oral, injected, or implanted hormonal method of contraception (see Section 5.1.3 for acceptable contraception methods)

4.5 STUDY ASSESSMENTS

All patients will be closely monitored for safety and tolerability during all cycles of therapy. Patients should be assessed for toxicity prior to each dose and dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Study treatment will be administered in 3-week (21-day) cycles (assuming there is no delay as a result of an adverse event).

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically-significant diseases, cancer history (including all prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) that are used by the patient within 7 days prior to the screening visit.

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

4.5.1.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality that is identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), patients will undergo a limited, symptom-driven physical examination that focuses on organ systems related to potential and ongoing adverse events and is based on the patient's clinical course during study treatment, the patient's medical history, and/or the known adverse event profiles of the study medications. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically-significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.1.3 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position.

4.5.1.4 Tumor and Response Evaluations

The baseline breast tumor must be >2 cm in diameter for *all* patients. Baseline tumor assessments will include a breast magnetic resonance imaging (MRI) scan and a clinical breast examination (CBE; including breast, axilla, and supraclavicular fossa). *If a patient has an allergy to an MRI contrast agent that cannot be managed with premedication per standard practice, then an ultrasound or molybdenum target mammography may be used.* Disease status should also be evaluated by additional conventional methods such as mammogram, ultrasound, computed tomography (CT) scans, or X-rays per local medical practice. A baseline bone scan is mandatory. In the

absence of radioactive isotopes, an MRI scan (with gadolinium enhancement if required) or positron emission tomography (PET) scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.

Prior to neoadjuvant treatment, the tumor must be physically marked per standard local practice (e.g., skin tattoo or surgical clip) so that the appropriate excision can be made should the patient experience complete clinical regression of the tumor prior to surgery (see Appendix 7, Appendix 8, and Appendix 9).

The axillary lymph nodes should be clinically evaluated at baseline in accordance with local practice and the findings should be recorded. For patients with clinically and/or ultrasound-suspicious axillary nodes at baseline, axillary staging should include a fine-needle aspiration or core biopsy sample collection performed prior to neoadjuvant therapy.

Surgical management options for axillary lymph nodes include SLNB sample collection prior to or after neoadjuvant treatment and ALND tissue collection of Level I and II lymphatics at the time of breast surgery. The choice of the axillary procedure will be based on the clinical status of the axilla, T stage, and local practice.

Patients will be evaluated by CBE during neoadjuvant treatment (Cycles 1–4) and a breast MRI scan and CBE will be repeated after completion of treatment in Cycle 4 (i.e., prior to surgery). In addition, disease status may be evaluated by additional conventional methods per local medical practice.

Consistency of consecutive CBEs, MRI scans, CT scans, mammograms, or X-rays should be ensured during all assessments for each patient with the same technique used to evaluate the target lesion throughout the treatment period. Tumor measurements should be made by the same investigator or radiologist for each patient during the study to the extent that this is feasible. In case of clinically-measurable superficial (such as skin) lesions, repeated photographs should be used to document the tumor response. These photographs must include a ruler for documentation purposes.

If the lesion shows clear signs of progression per RECIST v1.1 (see Appendix 4), the patient should be removed from study treatment and provided with local standard-of-care treatment.

Discovery of contralateral ductal carcinoma in situ during Cycles 1–4 will not be considered PD. However, invasive contralateral breast carcinoma will be considered PD.

4.5.1.5 Laboratory Assessments

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

- Hematology: hemoglobin, hematocrit, platelet count, WBC count, and ANC

- Serum chemistry

  Baseline: sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN or urea, creatinine, total protein, albumin, alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, total bilirubin, and direct bilirubin

  Subsequent timepoints: potassium, alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin if total bilirubin is > ULN

- Coagulation: INR and aPTT
- Pregnancy test

  Women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test performed within 7 days prior to randomization. Urine pregnancy tests will be performed within 7 days prior to specified subsequent visits (see Appendix 1). If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

- Urinalysis, *which may be performed by* dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination where applicable (e.g., if the *urinalysis* result is positive, then a microscopic examination should be performed; sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria)

Samples for the following laboratory tests will be sent to one or several central laboratories or to Roche for analysis:

- Mandatory tumor tissue sample obtained at screening for prospective central determination of HER2 status by IHC and ISH *and exploratory biomarker research:*

  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 or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals ≥2.0) by ISH prior to randomization. Paraffin-embedded tumor tissue block or a partial block must be obtained. If sites are unable to send a tissue block because of local regulations, at least *15* unstained, freshly cut slides should be sent for HER2 testing and exploratory biomarker research (see below). The slides should be cut from consecutive slices from the same block.

  Central laboratory confirmation of a positive HER2 status is required prior to randomization. The outcome of this assessment will be communicated to the investigator.

  After completion of HER2 testing for eligibility criteria, patient samples may also be tested with other HER2 assays to establish performance characteristics of these assays for diagnostic development *but if generated, these data will have no impact on the study eligibility of the patient. Additional testing will not be performed on patients who failed screening*.

- *Remaining t*umor tissue sample obtained *from enrolled patients* at screening *will be used* for exploratory research on candidate biomarkers; such analyses may include but will not be limited to the following: HER2/3 mRNA and/or protein,

PIK*3CA mutation*, PTEN*, PD-L1, CD8, and other biomarkers that are relevant to breast cancer*

- *Mandatory resection tissue specimen obtained at the time of surgery for determination of HER2 status and for assessment of exploratory biomarkers*

  A paraffin-embedded resection tissue block or up to 15 unstained, freshly-cut slides should be sent. The slides should be from consecutive slices from the same block.

- Serum samples for analysis of ATAs to pertuzumab
- Serum samples for exploratory research on candidate biomarkers; may include but will not be limited to the following: HER ligands and HER2 ECD
- Optional serum samples for analysis of pertuzumab pharmacokinetics, to be performed in a subset of approximately 50 patients in each treatment arm (see Section 4.5.1.6)

  The Informed Consent Form will contain a separate section that addresses optional collection of these samples.

- Optional tumor tissue and/or serum sample collection at the time of disease progression or recurrence

  A paraffin-embedded disease progression or recurrence tumor tissue block or up to 15 unstained, freshly-cut slides should be sent. The slides should be from consecutive slices from the same block.

  The Informed Consent Form will contain a separate section that addresses optional collection of these samples.

- Optional whole blood samples for DNA extraction for clinical genotyping

  The Informed Consent Form will contain a separate section that addresses collection of these samples for the Biomarker Sample Repository.

  Data arising from clinical genotyping will be subject to the following confidentiality standards: given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for specimens and associated data. Upon receipt by the Biomarker Sample Repository, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

Samples listed above will be destroyed at the end of the study, with the following exceptions:

- Tissue blocks that are submitted at baseline for eligibility screening and exploratory biomarker research will be returned in a batched manner to the sites after all patients have completed the neoadjuvant phase of the study. *All other tissue blocks that are submitted will be returned to the sites in batches at the latest 5 years after the last patient in.* 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.
- Serum samples for analysis of ATAs to pertuzumab, exploratory research on candidate biomarkers, optional serum samples, and optional whole blood samples for DNA extraction will be destroyed no later than 5 years after the date of final closure of the clinical database.

A patient's withdrawal from the study does not, by itself, constitute withdrawal of specimens collected under optional consent. Likewise, a patient's withdrawal from optional sample collection does not constitute withdrawal from the study.

Clinical responses will be assessed locally and not independently reviewed.

4.5.1.6 Pathologic Response Evaluation

Pathologic response (tpCR and bpCR) will be assessed with use of tumor tissue resection specimens that are obtained during surgery. All response evaluations will be assessed locally as outlined in Appendix 7, Appendix 8, and Appendix 9 and independently reviewed by an IRC in accordance with guidelines from a pathology manual that will be provided in a separate guidance document.

Copies of the pathology report(s) from the patient's primary (main) surgery must be submitted to the Sponsor within 6 weeks after the date of surgery. If additional information on lymph nodes at surgery is present in other reports, these should also be submitted to the Sponsor.

4.5.1.7 Diagnosis of Relapse or Recurrence

Recurrent disease includes local, regional, and distant recurrence and contralateral breast cancer. Wherever possible, maintain patients who are diagnosed with in situ breast disease or second (non-breast) malignancies in regular follow-up to fully capture any subsequent recurrent disease events. In cases of diagnostic doubt (e.g., ill-defined, palpable mass in an irradiated breast), histologic or cytologic confirmation of recurrence should be obtained whenever possible.

Some patients may develop a suspicious recurrence that quickly leads to death without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report for these patients.

The earliest date of diagnosis of recurrent disease should be used and recorded. This should be based on clinical, radiologic, histologic, or cytologic evidence. The date of disease recurrence should be reported as the date of first diagnosis of a lesion (i.e., an objective finding) and not the date of the occurrence of the first symptom.

Report all second primary malignancies whenever they occur during the study. Patients who receive a diagnosis with a second primary malignancy that does not require systemic therapy (i.e., chemotherapy, hormonal therapy, targeted therapy, etc.) and with no evidence of breast cancer recurrence will remain in the study and should continue with the study drug treatment in accordance with the protocol and schedule of activities (see Appendix 1) if considered by the investigator to be in the patient's best interest whenever possible.

The following events are NOT considered recurrent disease but must be recorded:

- Ipsilateral and contralateral lobular carcinoma in situ
- Ipsilateral and contralateral ductal carcinoma in situ
- Carcinoma in situ of the cervix
- Basal or squamous cell carcinoma of the skin

After recurrence, all patients should be followed for survival in accordance with the schedule of activities (see Appendix 1). Related serious adverse events and non-breast second primary malignancies (reportable as serious adverse events) should also be reported until the end of the study.

4.5.1.8 Pharmacokinetic Assessments

Blood samples for serial measurements of pertuzumab serum concentrations will be collected from a subset of 50 Chinese patients (50 will be capped through the IxRS system on a first come first serve basis) in accordance with the schedule of activities (see Appendix 1). One 2-mL sample will be collected at each timepoint (see sampling schedule in Appendix 2). The sampling timepoints will allow for an estimation of pertuzumab maximum concentration (C_{max}) values in Cycles 1, 2, 4, 10, and 15 and estimation of minimum concentration (C_{min}) values in Cycles 1, 2, 4, 10, and 15 at treatment completion or discontinuation (28 days after the last administration of study treatment and at 60–90 days after the last administration of study treatment).

The date and actual start and end times of each pertuzumab infusion and the date and actual time of each sample collection should be recorded on the PK sampling form. Any important information with regard to the sample or its collection (e.g., missed or late sample, hemolysis) should also be recorded.

4.5.1.9 Anti-Therapeutic Antibody Assessments

The sampling timepoints for the ATA assessment are prior to the first infusion on Day 1 of Cycles 4, 10, and 15 and at the treatment completion or discontinuation (28 days after last administration of study treatment and at 60–90 days after last administration of study treatment; see Appendix 3).

4.5.1.10 Cardiac Assessments

Electrocardiograms

Single 12-lead ECGs will be performed locally and assessed at the time of screening and otherwise as clinically indicated. The investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. For ECG tracings that will fade over time (e.g., ECGs on thermal paper), lasting legible copies should be filed together with the original.

Left Ventricular Ejection Fraction

LVEF will be assessed by ECHO (preferred) or MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

4.5.1.11 Assessments at Unplanned Visits

Assessments at any unplanned visits should be performed as clinically indicated.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening Assessments

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

Screening tests and evaluations will be performed within 28 days prior to enrollment, unless otherwise specified. Local hematology and chemistry assessments that are scheduled for Cycle 1, Day 1 must be performed within 7 days prior to randomization.

The following standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment do not need to be repeated for screening: bone scan (or MRI or PET scan), mammogram, ultrasound, breast MRI, chest X-ray, ECG, or ECHO or MUGA scan. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

See Appendix 1 for the Schedule of Activities to be performed during screening.

4.5.2.2 Assessments during Treatment

Scheduled study visits are based on a 3-week (21-day) cycle, with Cycle 1 beginning on Day 1. With the exception of Cycle 1, Day 1, all assessments should be performed within 3 days of the scheduled visit unless otherwise specified. Assessments that are scheduled on the day of study treatment administration should be performed prior to administration of the study treatment unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date.

With the exception of Cycle 1, Day 1, local hematology and chemistry assessments scheduled for Day 1 of all cycles must be performed within 3 days prior to study treatment administration. Results of local laboratory assessments must be reviewed and the review documented prior to study treatment administration.

See Appendix 1 for the Schedule of Activities to be performed during the treatment period.

4.5.2.3 Assessments at Treatment Completion or Discontinuation Visit

Patients may remain on the study treatment until disease progression (in the neoadjuvant setting) or disease recurrence (in the adjuvant setting) as assessed by the investigator, unacceptable toxicity, or completion of 17 cycles of HER2-targeted therapy. Patients who discontinue the study treatment will be asked to return to the clinic approximately 28 (±7) days after administration of the last dose of study treatment for the treatment discontinuation visit.

See Appendix 1 for the Schedule of Activities to be performed at the treatment completion or discontinuation visit.

4.5.2.4 Follow-Up Assessments

After the treatment completion or discontinuation visit, adverse events should be followed as outlined in Sections 5.5 and 5.6.

Patients will be followed for survival every 3 months (±28 days) for the first year and then every 6 months (±28 days) thereafter until disease progression or recurrence or until 5 years after randomization of the last patient, whichever occurs first.

See Appendix 1 for the Schedule of Activities during the follow-up of patients.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from the study treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue the study treatment or withdraw from the study at any time for any

reason. Reasons for discontinuation of study treatment or withdrawal from the study may include but are not limited to:

- 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

4.6.1.1 Discontinuation from Study Treatment

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

- Pregnancy
- Disease progression (in the neoadjuvant setting) or disease recurrence (in the adjuvant setting)
- Symptomatic LVSD (heart failure) at any point during the study
- Three intermittent dose delays as a result of an asymptomatic decrease in LVEF
- Withhold treatment administration during the study for more than two cycles
- Intercurrent, non–cancer-related illness that prevents continuation of protocol therapy or follow-up
- Major protocol violation that may jeopardize the patient's safety according to the Sponsor
- Repeated patient non-compliance with protocol requirements
- Changes in the patient's condition or study treatment-related toxicity such that continued participation in the protocol would compromise the patient's well-being, in the opinion of the investigator

Patients who discontinue study treatment prematurely will be asked to return to the clinic for a treatment completion or discontinuation visit (see Section 4.5.2.3) and may undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.1.2 Withdrawal from the Study

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. 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 and Site Discontinuation

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

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

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for the replacement of a site may include but are not limited to:

- 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 the study and all obligations have been fulfilled)*

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Management of Risks that are Associated with Pertuzumab and Trastuzumab

Specific instructions for the management of infusion hypersensitivity reactions (including anaphylaxis), symptomatic LVSD or asymptomatic decreases in LVEF, and HER2-related toxicities are described below.

5.1.1.1 Infusion-Associated Reactions, 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 very shortly after an infusion.

In general (and in common with other antibody-associated infusion reactions), pertuzumab and trastuzumab 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 trastuzumab therapy—the incidence and severity of such reactions are similar regardless of prior or concurrent treatment with trastuzumab.

The administration of pertuzumab and trastuzumab 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 30 minutes after the first and each $subsequent$ trastuzumab infusion. If the pertuzumab infusion is well tolerated during Cycle 1, the observation time can be decreased to 30 minutes for subsequent infusions.

Infusion of pertuzumab or trastuzumab should be slowed or interrupted if the patient experiences infusion-associated symptoms (e.g., fever, chills, headache, fatigue, pruritus, nausea, vomiting, and diarrhea). Supportive care with oxygen, β-agonists, antihistamines, antipyretics, and corticosteroids may help alleviate symptoms. All infusion-associated symptoms must be resolved before pertuzumab is administered. 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 the potential exists 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

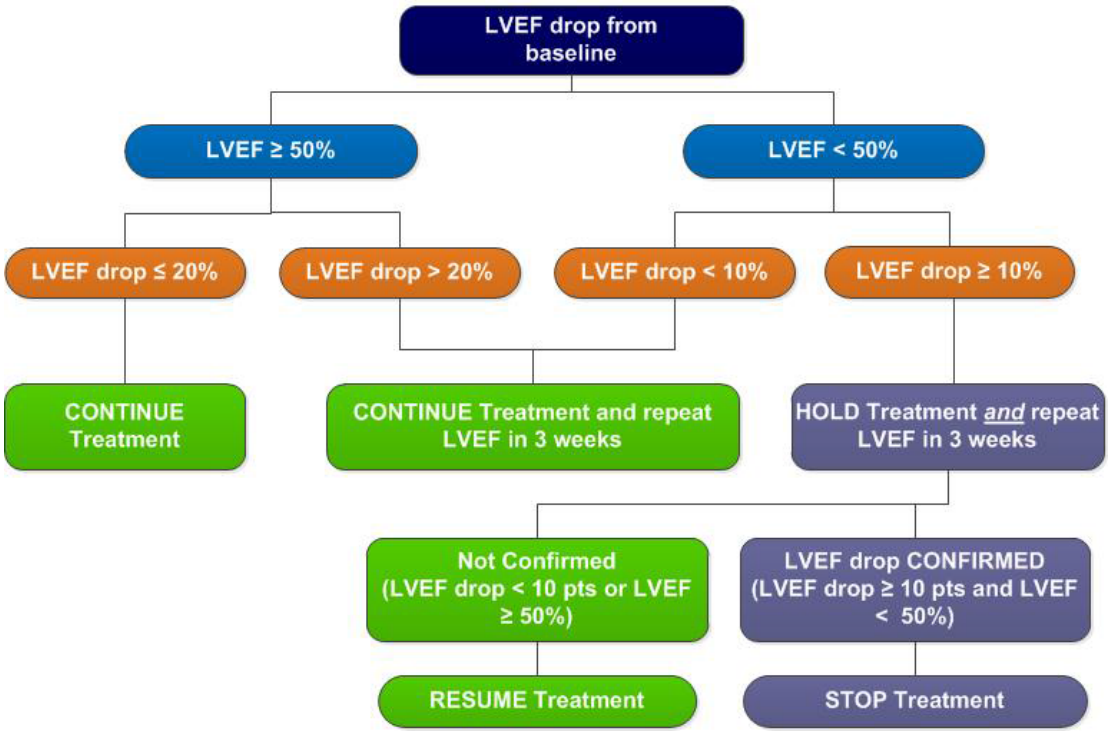
There is a risk of cardiac dysfunction with pertuzumab, as with trastuzumab, because each of these antibodies is directed at the HER2 receptor. A decrease in LVEF has been observed in patients who receive pertuzumab; however, the majority of patients show improvement or return to baseline function during follow-up (see Section 1.2.2.2).

All patients will undergo regular LVEF monitoring by ECHO or MUGA. Monitoring of LVEF is required while patients receive pertuzumab or placebo and trastuzumab as well as after treatment completion as per the Schedule of Activities (see Appendix 1).

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

If there is a significant asymptomatic decline in LVEF (LVEF decrease of $\geq$10 percentage points from baseline to an LVEF value of $<$50%), the patient must discontinue all study treatment. Figure 2 summarizes the management of study treatment for patients who have an asymptomatic decrease in LVEF. The decision to continue or stop the study treatment should be based on two factors: measured LVEF value and change in LVEF value from baseline.

Figure 2 Algorithm for the Continuation or Discontinuation of Study Treatment on the Basis of Asymptomatic Decline in LVEF



LVEF = left ventricular ejection fraction.

Note: Treatment refers to trastuzumab, pertuzumab or placebo, and (for neoadjuvant therapy) docetaxel.

5.1.1.3 Epidermal Growth Factor Receptor–Related Toxicities

Although pertuzumab targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., epidermal growth factor receptor [EGFR]), it may cause toxicities that are associated with the use of EGFR tyrosine kinase inhibitors. Diarrhea has been observed in approximately 60% of patients who were treated with pertuzumab in Phase II single-agent studies (up to 90% of patients who received pertuzumab in combination studies) and was reported as a Grade 1 or 2 in the majority of cases. For patients who experience diarrhea, early intervention with loperamide should be recommended and hydration considered.

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 who received pertuzumab in Phase II single-agent studies (up to 40% of patients who received pertuzumab in combination studies) and was generally reported as Grade 1 or 2 in severity.

5.1.2 Dosage Modification and Treatment Interruption or Discontinuation

5.1.2.1 Trastuzumab, Pertuzumab or Placebo, and Docetaxel

Docetaxel dosage modifications should be managed as per local practice. A stepwise dose reduction from 75 to 60 mg/m^2 is permitted. If a further reduction is required, the patient will be withdrawn from all study treatment and treated at the discretion of the investigator as clinically indicated. Once a dose reduction has occurred, the patient's dose should not be re-escalated to a higher one. Docetaxel dose delays will be allowed for myelosuppression, hepatic dysfunction, and other dose-limiting toxicities. If docetaxel must be delayed for a day or more, all study treatments should be delayed for the same time frame. If docetaxel is held for more than two cycles or needs to be permanently discontinued, the patient will be withdrawn from all study treatment.

Dosage modifications are not permitted for trastuzumab or pertuzumab. Actions to be taken for toxicities that are related to treatment with trastuzumab or pertuzumab are outlined in Table 1. If trastuzumab or pertuzumab/placebo must be delayed for a day or more, all study treatments should be delayed for the same time frame; thus, delays provided in Table 1 also apply to docetaxel.

Table 1 Actions to be Taken for Toxicities Related to Study Treatment

Toxicity	Action
Neutropenia	Withhold all study treatment for up to 6 weeks. If recovery to ANC $\geq$1000 cells/μL occurs within 6 weeks, resume all treatment. If recovery to ANC $\geq$1000 cells/μL does not occur within 6 weeks, discontinue all treatment.
Symptomatic LVSD (heart failure)	Discontinue all study treatment.
Asymptomatic decrease in LVEF	Follow instructions for withholding, 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	Withhold all study treatment for up to 6 weeks. If recovery to Grade $\leq$2 occurs within 6 weeks, resume all treatment. If recovery to Grade $\leq$2 does not occur within 6 weeks, discontinue all study treatment.

Table 1 Actions to be Taken for Toxicities Related to Study Treatment (cont.)

Toxicity	Action
Recurrence of other non-hematologic toxicities [a] upon rechallenge: Grade 3 or 4	Discontinue all study treatment.

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

Notes: Severity grades for all events are based on NCI CTCAE v4.0, with the exception of symptomatic LVSD, which should be graded according to NCI CTCAE v4.0 for "heart failure" (Grade 2, 3, 4, or 5) and the New York Heart Association classification (see Appendix 6). Study treatment refers to trastuzumab, pertuzumab/placebo, and (for neoadjuvant therapy) docetaxel.

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

5.1.2.2 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy

Dosage modification and treatment interruption or discontinuation are permitted for FEC chemotherapy as indicated in the relevant local label for each agent and will be managed in accordance with local practice.

5.1.3 Pregnancy and Contraception

Women who are not postmenopausal (< 12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus) must agree to use one highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception while administered the study treatment and for 7 months after the last dose of study treatment. Men who participate in the study must agree to use reliable and effective contraceptive measures while administered the study treatment and for 7 months after the last dose of the study treatment. Male study participants whose partners are pregnant should use condoms for the duration of the pregnancy.

Methods of birth control that result in a low failure rate (i.e., < 1% per year) when used consistently and correctly are considered highly effective forms of contraception. The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g., calendar, ovulation, symptothermal postovulation methods) and withdrawal are not acceptable methods of contraception
- Tubal ligation
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate); for female patients, the vasectomized male partner should be the sole partner

Alternatively, two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal intrauterine device or intrauterine system; consideration should be given to the type of device being used, as there are higher failure rates quoted for certain types (e.g., steel or copper wire)
- Condom with spermicidal foam, gel, film, cream, or suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are ineffective to prevent pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required.
A double-barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository.

5.1.4 Breastfeeding

It is not known whether trastuzumab or pertuzumab is excreted in human milk. As 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 trastuzumab therapy and not breastfeed for at least 7 months after the last dose of either monoclonal antibody. Therefore, during the FEC portion of treatment (in absence of the antibodies), patients should also not breastfeed during this time period.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events 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 adverse event is any untoward medical occurrence in a clinical investigation subject who is administered a

pharmaceutical product regardless of the causal attribution. Therefore, an adverse event can 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 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory test result 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 the study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to the assignment of the study treatment (e.g., invasive screening procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event 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 5.3.5.10)
- Results in persistent or significant disability or incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect in a neonate or infant born to a mother who is exposed to the study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical and/or 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 adverse event (rated as mild, moderate, or severe, or in accordance with NCI CTCAE v4.0; 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 adverse event that is recorded on the eCRF.

The investigator must report serious adverse events 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 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest must 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). Adverse events of special interest for this study include:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- 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 that indicate an infection in a patient who is exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab or placebo and trastuzumab

5.3 METHODS AND TIMING TO CAPTURE AND ASSESS SAFETY PARAMETERS

The investigator is responsible to ensure that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with the instructions provided in this section and Sections 5.4, 5.5, and 5.6.

For each adverse event that is 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 adverse events at each patient contact. All adverse events, 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 the study drug**, only serious adverse events that are caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of the study drug, all adverse events regardless of the relationship to the study drug will be reported until 28 days after administration of the last dose of the

study drug. After this period, investigators should report any serious adverse events or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted to elicit adverse event information during all patient evaluation timepoints. Examples of non-directive questions include:

"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 adverse event severity grading scale for the NCI CTCAE v4.0 will be used to assess adverse event severity. Use Table 2 to assess the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale ***for Events Not Specifically Listed in NCI CTCAE***

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive 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 NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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 one's self, 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

adverse event is considered 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 (where 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 who receive combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures to Record Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis with a start date that corresponds to the start date of the first symptom of the eventual diagnosis.

Infusion-Associated Reactions

Adverse events that occur during or on the same day as study drug infusion should be captured as a diagnosis of allergic reaction or infusion reaction rather than as individual signs and symptoms.

5.3.5.2 Adverse Events that Occur Secondary to Other Events

In general, adverse events that occur 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 adverse events that

occur 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 adverse events should be recorded separately on the Adverse Event eCRF if it is unclear whether the events are associated.

5.3.5.3 Persistent, Intermittent, or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, it should be recorded as a new event on the Adverse Event eCRF. The date that the event became serious should be recorded as the resolution date for the initial non-serious event and as the onset date for the new serious adverse event.

An intermittent adverse event is one that starts, stops, and then restarts within a 28-day time window. Such events should be recorded as one event.

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

5.3.5.4 Abnormal Laboratory Test Values

Not every laboratory test result abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is 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

- Is clinically significant in the investigator's judgment

  Note: For oncology studies, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory test result findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory test result abnormality should be classified as an adverse event.

If a clinically significant laboratory test result abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically-significant laboratory test result 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.

5.3.5.5 Abnormal Vital Sign Values

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

- Is 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
- Is clinically significant in the investigator's judgment

The investigator is responsible to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality 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 *(see Section 5.3.5.4 for details on recording persistent adverse events)*.

5.3.5.6 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 an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- 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 test values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to the progression of breast cancer should be recorded on the Study Completion/Early Discontinuation eCRF. All other deaths that occur during the study, regardless of the relationship to the 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. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death as a result of presumed cardiac causes in a patient with or without preexisting heart disease within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During the survival follow-up, deaths that are attributed to the progression of breast cancer should be recorded on the Study Completion/Early Discontinuation eCRF as well as on the Survival eCRF.

5.3.5.8 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 adverse event 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").

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression or recurrence of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression with the use of objective criteria. If there is any uncertainty as to whether an event is the result of disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device 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 adverse event
- Hospitalization due solely to the progression of the underlying cancer

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of the study drug should be recorded on the Adverse Event eCRF. If the associated adverse event 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).

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

Symptomatic LVSD (heart failure) should be reported as a serious adverse event. If the diagnosis is symptomatic LVSD, it should be reported as such and not as individual signs and symptoms thereof. Symptomatic LVSD should be graded in accordance with the NCI CTCAE v4.0 for "heart failure" (Grade 2, 3, 4, or 5) and the New York Heart Association (NYHA) classification (see Appendix 6). "Left ventricular systolic dysfunction" should not be used to describe symptomatic dysfunction as per the NCI CTCAE v4.0.

Symptomatic LVSD that occurs during the study must be reported irrespective of the causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

Asymptomatic decrease in LVEF should not be reported as an adverse event since LVEF data are collected separately on the eCRF. Exceptions to this rule are as follows:

- Asymptomatic decrease in LVEF of ≥ 10 percentage points from baseline to an LVEF of $< 50\%$ must be reported as an adverse event with the term of "ejection fraction decreased" as per the NCI CTCAE v4.0.
- Asymptomatic decrease in LVEF that requires treatment or leads to a discontinuation of pertuzumab or placebo and trastuzumab must also be reported as an adverse event on the eCRF.

Table 3 summarizes the reporting conventions for asymptomatic decrease in LVEF or symptomatic LVSD.

Table 3 Reporting Conventions for Asymptomatic Decrease in LVEF or Symptomatic LVSD

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decrease in LVEF of < 10 percentage points from baseline or to an LVEF ≥ 50%	No additional reporting required; LVEF results to be reported on eCRF	NA	NA
Asymptomatic decrease in LVEF of ≥ 10 percentage points from baseline to an LVEF < 50%	AE [a] (eCRF AE eForm)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decrease in LVEF requiring treatment or leading to discontinuation of pertuzumab/placebo and trastuzumab	AE (eCRF AE eForm) and Complete SAE form and indicate as AESI with expedited reporting (see Section 5.4.2)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Symptomatic LVSD (congestive heart failure)	AE (eCRF AE eForm) and SAE (SAE form) with expedited reporting (see Section 5.4.2)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; AESI = adverse event of special interest; eForm = electronic form; eCRF = electronic Case Report Form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

Note: Any symptomatic LVSD event must be reported as "heart failure."

[a] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

Refer to the algorithm (see Figure 2) when deciding whether to initiate, continue, or discontinue anti-HER2 study treatment on the basis of LVEF assessment in asymptomatic patients.

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 study. 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 *(see Section 5.4.2 for further details)*
- Adverse events of special interest *(see Section 5.4.2 for further details)*
- Pregnancies *(see Section 5.4.3 for further details)*

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 with the inclusion of recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority, Institutional Review Board (IRB), and Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor (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., Ph.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 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 Adverse Events of Special Interest

5.4.2.1 Events that Occur prior to Initiation of Study Drug

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events that are caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event/Adverse Event of Special Interest CRF and Fax Coversheet 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) with use of the fax numbers provided to investigators (see "Protocol Administrative and

Contact Information & List of Investigators"). Patients who undergo screening procedures but do not enroll in the study will only have serious adverse events recorded in the Roche Drug Safety database and not in the study's clinical database.

5.4.2.2 Events that Occur after Initiation of Study Drug

After initiation of the study drug, serious adverse events and adverse events of special interest will be reported until study completion. 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 Serious Adverse Event/Adverse Event of Special Interest CRF and Fax Coversheet 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) with use of 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 after study completion 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 *Clinical Trial Pregnancy Reporting Form* should be completed *and submitted to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy)*, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators*. 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 serious adverse events 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 and/or birth defect in the child) should be reported on the Adverse Event eCRF. Additional information on any pertuzumab-exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months after the infant's birth).

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet 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) with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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 serious adverse event (as the Sponsor considers abortions to be medically significant events), 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 and/or Birth Defects

Any congenital anomaly and/or birth defect in a child that is born to a female patient or a female partner of a male patient who is exposed to the study drug should be classified as a serious adverse event, 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 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 that are considered related to the study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (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 that are reported during the study should be followed until the pregnancy outcome *(see Section 5.4.3)*. 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 serious adverse events, adverse events of special interest, 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) to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

Upon completion of the study, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any serious adverse event or other adverse event of concern that occurs at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly and/or birth defect in a subsequently-conceived offspring of a patient who participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest 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 the reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events with use of the following reference documents:

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

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 to upgrade by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A total of 328 patients will be randomized into the study in a ratio of 2:1 to pertuzumab (Arm A) or placebo (Arm B), respectively. This will provide 85% power to detect an absolute increase in tpCR rate of 15% in the pertuzumab arm compared with the placebo arm at a two-sided significance level of 5%, assuming the tpCR rate is 20% in the placebo arm.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, duration of the follow-up, discontinuation from the study, and the 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

Demographic and baseline characteristics such as age, weight, ECOG Performance Status, ER and PgR status, HER2 status, and history of breast cancer will be summarized by treatment arm.

Descriptive statistics (mean, median, SD, 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 ITT principle, with patients grouped by the treatment assigned at the time of randomization. For DFS, only patients who undergo surgery will be included in the analysis. For clinical response rates, only patients with measurable disease at baseline will be included in the analysis.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is tpCR, defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes after completion of neoadjuvant therapy and surgery (i.e., ypT0/is, ypN0 in accordance with the current AJCC staging system) as assessed by the IRC. The primary analysis will be performed when all patients *who are eligible for surgery* have completed the*ir surgical* treatment *with an assessment of pathological response*. The analysis will be based on the ITT population with patients grouped by the treatment assigned at the time of randomization. In the ITT population, patients whose tpCR assessment is missing or invalid are counted as not achieving tpCR.

The tpCR rate as assessed by the IRC will be summarized for each treatment arm and 95% CIs will be calculated with the Clopper-Pearson method. The two-sided Cochran-Mantel-Haenszel test, stratified by disease category (early-stage or locally advanced) and hormone receptor status (positive for ER and/or PgR or negative for both) will be used to compare the tpCR rate between the two treatment arms. An unadjusted Fisher exact test result will also be provided. Finally, the difference in tpCR rate and associated 95% CIs will be provided with use of the Hauck-Anderson method.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy outcome measures in this study are tpCR as assessed by the local pathologist, bpCR as assessed by the IRC, bpCR as assessed by the local pathologist, clinical response, EFS, DFS, and overall survival.

6.4.2.1 Total Pathologic Complete Response Rate as Assessed by the Local Pathologist

tpCR rate as assessed by the local pathologist will be evaluated with methods that are similar to those described for the primary efficacy endpoint.

6.4.2.2 Breast Pathologic Complete Response Rate as Assessed by the Independent Review Committee

bpCR is defined as the absence of any residual invasive cancer on the hematoxylin and eosin evaluation of the resected breast specimen after completion of neoadjuvant therapy and surgery (i.e., ypT0/is in accordance with the current AJCC staging system). bpCR rate as assessed by the IRC will be evaluated with use of methods that are similar to those described for the primary efficacy endpoint.

6.4.2.3 Breast Pathologic Complete Response Rate as Assessed by the Local Pathologist

bpCR rate as assessed by the local pathologist will be evaluated with methods that are similar to those described for the primary efficacy endpoint.

6.4.2.4 Response Rates

Clinical response rates that include the proportions of patients with a CR, PR, stable disease, or PD will be determined by the investigator during Cycles 1–4 (i.e., prior to surgery) on the basis of RECIST v1.1. ORR is defined as the proportion of patients who achieve a CR or PR as the best tumor response during the neoadjuvant period. No confirmation is required for objective response. Only patients with measurable disease at baseline will be included in the analysis. The methods for data analysis are similar to those described for the primary efficacy endpoint.

6.4.2.5 Event-Free Survival

EFS is defined as the time from randomization to the first documentation of one of the following events:

- Disease progression (before surgery) as determined by the investigator with use of RECIST v1.1

  Any evidence of contralateral disease in situ will not be identified as PD.
- Disease recurrence (local, regional, distant, or contralateral) after surgery
- Death from any cause

Patients who have not had an event at the time of the analysis will be censored as of the date they were last known to be alive and event free.

The two-sided log-rank test, stratified by disease category (early-stage or locally advanced) and hormone-receptor status (positive for ER and/or PgR or negative for both) will be used to make an exploratory comparison of EFS between the two treatment arms. The Kaplan-Meier approach will be used to estimate 3-year EFS rates for each treatment arm. The stratified Cox proportional hazards model will be used to estimate the HR between the two treatment arms (i.e., the magnitude of treatment effect) and its 95% CI.

6.4.2.6 Disease-Free Survival

DFS is defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of one of the following events:

- Disease recurrence (local, regional, distant, or contralateral) after surgery

  Any evidence of contralateral disease in situ will not be identified as disease recurrence.
- Death from any cause

Only patients who undergo surgery will be included in the analysis. It is assumed that all patients who undergo surgery are disease free and; hence, patients are known to be disease free if they have undergone surgery and no recurrence of disease is reported thereafter. *Data from p*atients who have not had an event at the time of the analysis will be censored as of the date they were last known to be alive and event free. The

methods for data analysis are similar to those described for EFS. Note that the analysis for DFS is exploratory because of the non-randomized patient population.

6.4.2.7 Overall Survival

Overall survival is defined as the time from randomization to death from any cause. *Data from p*atients who are alive at the time of the analysis will be censored as of the last date they were known to be alive. The methods for data analysis are similar to those described for EFS.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety analysis population, which will consist of all patients who received at least one dose of study drugs and patients will be grouped by the treatment they actually received. *The safety analyses will be performed at the same time as the primary efficacy analysis, the final analyses, and when all patients have completed the treatment completion or study discontinuation visit.*

6.5.1 Study Drug Exposure

The numbers of patients who experience any dose interruption (including dose delays), dose modification, and 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

Safety will be assessed through summaries of adverse events, serious adverse events, deaths, and Grade 3 or 4 adverse events. Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms. All adverse events that occur on or after the date of the first study drug administration will be summarized by mapped term, appropriate thesaurus levels, and toxicity grade based on NCI CTCAE v4.0.

Deaths that are reported during the study treatment period and those reported during the follow-up (after treatment discontinuation) will be summarized by treatment arm.

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 asymptomatic decrease in LVEF (defined as an absolute decrease of ≥ 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 with use of the NCI CTCAE v4.0 for each treatment arm. Changes from baseline will be presented in shift tables for selected laboratory test result assessments.

6.6 EXPLORATORY ANALYSES

6.6.1 Exploratory Pharmacokinetic Analyses

Observed C_{max} and C_{min} values will be summarized for pertuzumab at each specified sampling timepoint. Descriptive statistics will include mean, median, SD, CI, and range of values as appropriate.

Graphical plots and comparisons of the descriptive statistics will be made between observed serum pertuzumab concentrations in this study and observed serum pertuzumab concentrations in studies that are not conducted in China.

Graphical plots and comparisons of the descriptive statistics will be made between observed serum pertuzumab concentrations in the neoadjuvant and adjuvant phase in this study. Additionally, observed serum pertuzumab concentrations in this study will also be compared with the observed serum pertuzumab concentrations in the adjuvant phase of the PK substudy in Chinese patients from Study BIG 4-11/BO25126/TOC4939g.

In addition, exploratory analyses will be performed to assess any correlation between HER2 ECD and the pharmacokinetics of pertuzumab.

6.6.2 Sensitivity and Subgroup Analyses

Sensitivity analyses will be performed for tpCR rate to ascertain whether the magnitude of the effectiveness of the addition of pertuzumab might differ by patient subgroups.

Variables to be considered to define subgroups of interest include stratification factors as well as other disease- or patient-related prognostic or predictive factors. The following factors will be examined in preplanned subgroup analyses:

- Menopausal status at randomization
- Tumor size
- Lymph nodes
- Histological grade
- Disease category
- Hormone receptor status (ER, PgR)

Additional factors may also be considered.

6.6.3 Biomarker Analyses

The correlation between baseline molecular biomarkers and efficacy outcomes will be evaluated. Biomarkers may include but are not limited to the status of HER receptors, HER ligands, HER2 ECD, and other biomarkers that are relevant for the HER family pathway. Special emphasis will be placed on biomarkers that have shown an association with clinical outcome in patients who were treated with pertuzumab in previous studies. Efficacy outcomes that are considered for this analysis may include tpCR, EFS, and DFS.

If possible, biomarker levels at baseline will be compared with biomarker levels in samples that are collected at the time of surgery from patients with residual disease.

6.6.4 Anti-Therapeutic Antibody Analyses

To determine whether ATAs to pertuzumab are formed as a result of the administration of study treatment, serum samples will be collected to test for the presence of ATAs to pertuzumab from all randomized patients at screening and after treatment.

The impact of ATAs to pertuzumab on pharmacokinetics, safety, and efficacy will be further explored in this study.

6.7 INTERIM ANALYSES

There is no interim analysis planned for the primary efficacy outcome measure tpCR. EFS and DFS data will be summarized descriptively *at the time of the primary efficacy analysis*. Note that a final analysis of EFS, DFS, and overall survival will be performed at the end of the study approximately 5 years after randomization of the last patient.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for the data management of this study with inclusion of quality checking of the data. Data that are entered manually will be collected via EDC with the use of 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. Central laboratory data will be sent directly to the Sponsor with use of 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of 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) that are 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, patient-reported outcomes, 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 study.

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 that are 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 with direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB and/or 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 an investigational 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 with regard to computerized systems that are used in clinical research. An acceptable computerized data collection system allows for the 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 that pertain 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 Child’s Assent or 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 and/or EC submission. The final IRB- and/or EC-approved consent forms must be provided to the Sponsor for health authority submission purposes in accordance with local requirements.

The Informed Consent Form will contain a separate section that addresses the use of the 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 will 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 and/or EC-approved consent forms must be provided to the Sponsor for health authority submission purposes.

Patients must re-consent to the most current version of the consent forms (or to a significant new information and/or findings addendum in accordance with applicable laws and IRB and/or EC policy) during their participation in the study. For any updated or revised consent forms, the case history or clinical records for each patient will document the informed consent process and that written informed consent was obtained with use of the updated and/or 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 and/or EC by the Principal Investigator and reviewed and approved by the IRB and/or EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB and/or EC.

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

In addition to the requirements to report all adverse events to the Sponsor, investigators must comply with the requirements to report serious adverse events to the local health authority, IRB, and EC. Investigators are responsible to ensure that such reports are reviewed and processed in accordance with health authority requirements and the

policies and procedures established by their IRB and/or 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 datasets that are transmitted to any Sponsor location.

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

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data that are generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB and 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., approximately 5 years after the date of randomization of the last patient).

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 and/or EC and governmental approval. In addition, at the end of the study, the investigator will receive

the patient data, which includes an audit trail that contains a complete record of all changes to the data.

9.2 *PROTOCOL DEVIATIONS*

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB and/or EC in accordance with established IRB and/or EC policies and procedures.

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 and ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Randomization will occur through an IxRS (see Section 4.2). Central facilities will be used for specified laboratory tests. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Data for this study will be recorded via an EDC system using eCRFs. In no case is the eCRF to be considered as the source data for this study (see Section 7.3).

An IRC that consists of independent experts who are not involved in the study (including approximately *three* pathologists) will evaluate pathologic response. The details of the composition, roles, and responsibilities of the IRC will be provided in a charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:
http://www.roche.com/dam/jcr:1c46aa73-cea0-4b9b-8eaa-e9a788ed021b/en/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific meetings. *For all clinical studies conducted in patients that involve an IMP for which a marketing*

authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies conducted in patients that involve an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

*T*he investigator *must* agree to submit all manuscripts or abstracts to the Sponsor prior to submission *for publication or presentation*. This allows the Sponsor to protect proprietary information and provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support only publication of multicenter studies 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 that originate from the use of the 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 and/or EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB and/or EC and regulatory authorities (as locally required) before implementation of any changes except for changes that are necessary to eliminate an immediate hazard to patients or changes that involve only logistical or administrative aspects (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Alm El-Din MA, Taghian AG. Breast conservation therapy for patients with locally advanced breast cancer. Semin Radiat Oncol 2009;19:229–35.

Bartlett J, Munro A, Cameron DA, et al. Subset analyses from the NEAT study [abstract]. San Antonio Breast Cancer Symposium (SABCS) 2008: abstract 49.

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 [abstract]. Proc Am Soc Clin Oncol 2007: abstract 1004.

Baselga J, Cortes J, Fumoleau P, et al. Pertuzumab and trastuzumab: re-responses to 2 biological agents in patients with HER2-positive breast cancer which had previously progressed during therapy with each agent given separately – a new biological and clinical observation [abstract]. San Antonio Breast Cancer Symposium (SABCS) 2009:abstract 5114.

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

Baselga J, Cortés J, Im SA, et al. S5-Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC) [abstract]. San Antonio Breast Cancer Symposium (SABCS) 2012b.

Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019–27.

Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676–85.

Chinese Cancer Registry Annual Report. Military Medical Science Press, Beijing, 2012.

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

Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5. Lyon, France: International Agency for Research on Cancer.

Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.

Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672–85.

Fisher ER, Wang J, Bryant J, et al. Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer 2002;95:681–95.

Fujiwara K, Kohno I, Tanaka K, et al. Phase II dose escalation: a novel approach to balancing efficacy and toxicity of anticancer agents. Japanese Docetaxel Ovarian Cancer Study Group. Anticancer Res 1999;19:639–44.

Gelmon KA, Fumoleau P, Verma S, et al. Results of a phase II trial of trastuzumab (H) and pertuzumab (P) in patients (pts) with HER2-positive metastatic breast cancer (MBC) who had progressed during trastuzumab therapy [abstract]. Proceedings of the American Society of Oncology 2008, abstract 1026.

Gennari A, Sormani MP, Pronzato P, et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. J Natl Cancer Inst 2008;100:14–20.

Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, Phase 2 trial. Lancet Oncol 2012;13:25–32.

Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, Phase 2 randomised trial. Lancet Oncol 2016:17:791–800.

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

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

Kaufmann M, Hortobagyi GN, Goldhirsch A, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006;24:1940–9. Erratum in: J Clin Oncol 2006;24:3221.

Kurosumi M. Significance of histological evaluation in primary therapy for breast cancer-recent trends in primary modality with pathological complete response (pCR) as endpoint. Breast Cancer 2004;11:139–47.

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 as first-line treatment: the M77001 Study Group. J Clin Oncol 2005;23:4265–74.

Mauri D, Pavlidis N, Loannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. J Natl Cancer Inst 2005;97:188–94.

Pegram MD, Pietras R, Bajamonde A, et al. Targeted therapy: wave of the future. J Clin Oncol 2005;23:1776–81.

Perez EA, Suman VJ, Davidson NE, et al. Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial [abstract]. San Antonio Breast Cancer Symposium (SABCS), December 2009, abstract 80.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–72.

Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate and fluorouracil as adjuvant therapy for early breast cancer. N Engl J Med 2006;355:1851–62.

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. Breast cancer biomarkers and HER2 testing after 10 years of anti-HER2 therapy. Drug News Perspect 2009;22:93–106.

Sato N, Sano M, Tabei T, et al. Combination docetaxel and trastuzumab treatment for patients with HER-2-overexpressing metastatic breast cancer: a multicenter, phase-II study. Breast Cancer 2006;13:166–71.

Schneeweiss A, Chia S, Hickish T, et al. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: A Randomized phase II study (TRYPHAENA) [abstract]. Cancer Res 2011;71:abstract S5–6.

Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase III cardiac safety study (TRYPHAENA). Ann Oncol 2013:24:2278–84.

Slamon DJ, Clark GM, Wong SG, et al. Human 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, Shal S, et al. Use of chemotherapy plus monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.

Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER-2 positive metastatic breast cancer. N Engl J Med 2015;372:724–34.

Untch M, Eidtmann H, du Bois A, et al. Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer results of a phase I trial. Eur J Cancer 2004;40:988–97.

Walshe JM, Denduluri N, Berman AW, et al. A phase II trial with trastuzumab and pertuzumab in patients with HER2-overexpressed locally advanced and metastatic breast cancer. Clin Breast Cancer 2006;6:535–9.

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;33:655.

Appendix 1
Schedule of Activities

		Neoadjuvant Treatment				Pre-Surgery	Surgery	Adjuvant Treatment				Treatment Completion/ Discontinuation [a]	Follow-Up [b]
								FEC			HER2-Targeted		
Cycle	Screening	1	2	3	4	4	4	5 [c]	6	7	8–20		
Day	–28	1	1	1	1	22	22–35	1	1	1	1		
Informed consent [d]	x												
Demographic data	x												
General medical history	x												
Complete physical examination [e]	x							x				x	x
Limited physical examination [f]		x	x	x	x				x	x	x		
Vital signs [g]	x	x	x	x	x			x	x	x	x	x	
Weight [h]	x	x	x	x	x			x	x	x	x	x	
Height [h]	x												
ECOG Performance Status	x											x	
Hematology [i]	x	x	x	x	x			x	x	x	x	x	
Chemistry [j]	x	x						x				x	
Limited chemistry [k]			x	x	x				x	x	x		
INR and aPTT	x							x					
Urinalysis [l]	x							x					
Pregnancy test [m]	x			x					x		x [n]	x	x [n]
Bone scan [o]	x [p]												
Breast MRI scan [p]	x					x							

Appendix 1
Schedule of Activities (cont.)

		Neoadjuvant Treatment				Pre-Surgery	Surgery	Adjuvant Treatment				Treatment Completion/ Discontinuation [a]	Follow-Up [b]
								FEC			HER2-Targeted		
Cycle	Screening	1	2	3	4	4	4	5 [c]	6	7	8–20		
Day	–28	1	1	1	1	22	22–35	1	1	1	1		
Mammogram [p] (and ultrasound as per local practice)	x	x										x	x
Additional tumor assessments		x [q]											
Clinical tumor assessment/breast examination [r]	x	x	x	x	x	x		x	x	x	x [s]	x	x
Placement of skin tattoo and/or surgical clip at primary tumor site [t]	x												
Chest X-ray [u]	x [p]												
12-Lead ECG [v]	x [p]							x			x [w]	x	
ECHO or MUGA scan [x]	x [p]		x [y]		x [y]			x [z]			x [y, aa]	x [bb]	x [cc]
Serum PK sample (optional) [dd, ee]		x	x		x						x [ff]	x	x [gg]
Serum sample for HER2 ECD, HER ligands, and other exploratory biomarkers (mandatory) [ee]	x						x [hh]						
Serum sample for antibodies to pertuzumab (mandatory) [ee]	x				x						x [ff]	x	x [gg]
Whole blood sample for clinical genotyping (optional) [ii]	x												

Appendix 1
Schedule of Activities (cont.)

		Neoadjuvant Treatment				Pre-Surgery	Surgery	Adjuvant Treatment				Treatment Completion/ Discontinuation [a]	Follow-Up [b]
								FEC			HER2-Targeted		
Cycle	Screening	1	2	3	4	4	4	5 [c]	6	7	8–20		
Day	–28	1	1	1	1	22	22–35	1	1	1	1		
Tumor tissue collection for determination of HER2 status [jj] and exploratory biomarkers (mandatory)	x						x [kk]						
Tumor hormone receptor status	x												
Pathologic response assessment							x [ll]						
Tumor tissue and/or serum sample collection at the time of disease progression or recurrence (optional) [mm]		x											
Trastuzumab administration [nn]		x	x	x	x						x		
Pertuzumab or placebo administration [oo]		x	x	x	x						x		
Docetaxel administration [pp]		x	x	x	x								
FEC administration [qq]								x	x	x			
Adverse events [rr]	x	x	x	x	x	x	x	x	x	x	x	x	x [rr]
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	
Survival follow-up and anti-cancer treatments													x

Appendix 1
Schedule of Activities (cont.)

5-FU = 5-fluorouracil; AE = adverse event; CT = computed tomography; ECD = extracellular domain; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; HER = human epidermal growth factor receptor; IHC = immunohistochemistry; IRC = Independent Review Committee; ISU = in situ hybridization; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography; PK = pharmacokinetic; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all visits and assessments should be performed within 3 days of the scheduled visit date, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used; such tests do not need to be repeated for screening.

[a] The treatment completion/discontinuation visit will optimally be scheduled for 28 (±7) days after the last dose of study treatment.

[b] After treatment completion/discontinuation, follow-up information will be collected every 3 months (±28 days) for the first year and then every 6 months (± 28 days) thereafter, until disease progression or recurrence or until 5 years after randomization of the last patient, whichever occurs first.

[c] Cycle 5 administration should not occur until 2 weeks after surgery.

[d] Written informed consent must be obtained before any study-specific screening assessments are performed.

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Consists of a symptom-driven physical examination that focuses on organ systems related to potential and ongoing adverse events and is based on the patient's clinical course during study treatment, the patient's medical history, and/or the known adverse event profiles of the study medications. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Includes temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be entered into the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Weight is to be measured on Day 1 of each cycle and compared with baseline. If ±10% variation occurs, trastuzumab and chemotherapeutic doses will be recalculated. Height is to be measured at baseline and should be remeasured if the investigator thinks it is possible that the patient's height may have changed.

[i] Includes hemoglobin, hematocrit, platelet count, WBC count, and absolute neutrophil count. Hematologic evaluations should be completed and reviewed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before). At baseline, hematologic evaluations should be completed

and reviewed within 7 days prior to study drug dosing. Additional assessments may be performed as clinically indicated. For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until resolution of the AE (Grade $\leq$1 or baseline).

[j] Includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN or urea, creatinine, total protein, albumin, alkaline phosphatase, ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin, and direct bilirubin. At baseline, chemistry evaluations should be completed and reviewed within 7 days prior to study drug dosing. Chemistry evaluations should be completed and reviewed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before). Additional assessments may be performed as clinically indicated. For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until resolution of the AE (Grade $\leq$1 or baseline).

[k] Includes potassium, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin if total bilirubin is $>$ULN, and other tests as clinically indicated. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] *Urinalysis, which may be performed by* dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination *when applicable* (*e.g., if the urinalysis is positive;* sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

[m] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test within 7 days prior to randomization. Urine pregnancy tests will be performed within 7 days prior to the specified subsequent visits with results available prior to dosing. If a urine pregnancy test resu is positive, it must be confirmed by a serum pregnancy test.

[n] Perform at Cycles 9, 12, 15, and 18, at 3 and 6 months after the last dose of study treatment and as clinically indicated. A urine β-HCG test may be performed at these cycles; however, all positive urine pregnancy test results must be confirmed by a serum β-HCG test.

[o] In the absence of radioactive isotopes, an MRI scan (with gadolinium enhancement if required) or PET scan is an acceptable form of assessment of the skeleton for the presence of bone metastases.

[p] Standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment do not need to be repeated for screening.

[q] Additional conventional methods of tumor assessments, such as MRI, CT scans, mammograms, ultrasound, or X-rays, as per local medical practice, may be used to evaluate disease status throughout the study.

[r] Clinical tumor assessment will be performed as per local medical practice based on the principles of RECIST Version 1.1 criteria. Perform axillary node examination and management per Section 4.4.1 (Axillary Management) at surgery.

[s] During the adjuvant treatment period, patients should be assessed for recurrence at least every 3 months (*i.e.,* Cycle 9, Cycle 13, Cycle 17, *etc.* and at the study completion or early termination visit*)*.

[t] Prior to neoadjuvant treatment, the tumor must be marked using local standard methods (e.g., skin tattoo or surgical clip) so that the appropriate excision can be made should the patient experience complete clinical regression of the tumor prior to surgery (see Appendix 8 for more details).

[u] If a chest X-ray is not possible, an MRI or PET scan is acceptable.

Appendix 1
Schedule of Activities (cont.)

[v] Additional ECGs to be performed as clinically indicated.

[w] Perform at Cycles 8, 12, 16, and 20 and as clinically indicated.

[x] LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[y] Perform between Days 15 and 21 (inclusive) to allow for evaluation of the results before the next treatment cycle (or before surgery).

[z] Perform within 7 days prior to Cycle 5 dosing.

[aa] Perform at Cycles 8, 11, and 20.

[bb] Perform at the treatment completion/discontinuation visit if not performed within the previous 6 weeks.

[cc] Perform every 6 months for 2 years after study drug discontinuation, then annually for an additional 2 years. Report any cardiac events until the end of the study.

[dd] Samples should be obtained from a subset of approximately 50 patients who are enrolled in sites in China and who have signed the separate consent to participate.

[ee] Samples should be obtained *only from randomized patients and* in according with the schedule outlined in Appendix 2 or Appendix 3.

[ff] Perform at Cycles 10 and 15, as outlined in Appendix 2 and Appendix 3.

[gg] Samples should be obtained 60–90 days after the last dose of study treatment.

[hh] Samples to be taken at surgery or 24 hours prior to surgery, as outlined in Appendix 2.

[ii] Samples should be obtained only from patients who sign the separate consent to donate samples to the Biomarker Sample Repository.

[jj] HER2-positive breast cancer must be confirmed by a Sponsor-designated central laboratory as 3+ score by IHC in $>10\%$ of immunoreactive cells and/or HER2 gene amplification (ratio of HER2 gene signals to centromere 17 signals ≥ 2.0) by ISH prior to randomization. Archival tumor samples or samples obtained from primary sites are acceptable. If submission of tumor blocks or partial blocks is not a feasible alternative, *15* unstained freshly cut slides should be sent. The slides should be from consecutive slices from the same block.

[kk] *Samples from surgical resection specimens should be submitted from all patients.* For patients with residual disease, tissue samples obtained from resection specimen (blocks preferred) will be collected for exploratory biomarker analyses *for patients who achieve pCR the (former) tumor bed may be analyzed, if applicable. Up to 15 slides should be submitted for HER2 assessment and biomarker analysis.*

[ll] To be assessed locally and independently reviewed by the IRC, using the resected tumor according to guidelines provided in Appendix 7, Appendix 8, and Appendix 9.

[mm] Samples should be obtained only from patients who sign the separate consent to participate. *Up to 15 slides should be submitted for HER2 assessment and biomarker analysis.*

[nn] Patients will receive trastuzumab by IV infusion in 3-week cycles, as neoadjuvant treatment (8 mg/kg loading dose for Cycle 1, followed by

6 mg/kg for Cycles 2–4) and as adjuvant treatment (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9–20).

[oo] Patients in Arm A will receive pertuzumab by IV infusion in 3-week cycles, as neoadjuvant treatment (840 mg loading dose for Cycle 1, followed by 420 mg for Cycles 2–4) and as adjuvant treatment (840-mg loading dose for Cycle 8, followed by 420 mg for Cycles 9–20). Patients in Arm B will receive placebo by IV infusion in 3-week cycles, as neoadjuvant treatment (Cycles 1–4) and as adjuvant treatment (Cycles 8–20).

[pp] Patients will receive docetaxel (75 mg/m^2) by IV infusion every 3 weeks for Cycles 1–4.

[qq] Patients will receive 500–600 mg/m^2 5-FU, 90–120 mg/m^2 epirubicin, and 500–600 mg/m^2 cyclophosphamide by IV infusion every 3 weeks for Cycles 5–7.

[rr] 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. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, investigators should report any serious adverse events or other adverse events of concern that are believed to be related to prior treatment with study drug. 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 study-related procedures until a final outcome can be reported. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in this study.

Appendix 2
Schedule of Biomarker and Pharmacokinetic Activities

Visit	Timepoint	Sample Type
Baseline (Day −14)	NA	HER2 ECD, HER ligands, and other biomarkers (serum)
Day 1 of Cycles 1, 2, and 4	Prior to the first infusion	Pertuzumab PK (serum)
	After the last infusion	Pertuzumab PK (serum)
Surgery	At surgery or 24 hours prior to surgery	HER2 ECD, HER ligands, and other biomarkers (serum)
Day 1 of Cycles 10 and 15	Prior to the first infusion	Pertuzumab PK (serum)
	After the last infusion	Pertuzumab PK (serum)
Treatment completion/ discontinuation visit (28 days after the last dose of study treatment)	NA	Pertuzumab PK (serum)
Follow-up visit (60–90 days after the last dose of study treatment)	NA	Pertuzumab PK (serum)

ECD = extracellular domain; HER = human epidermal growth factor receptor; NA = not applicable; PK = pharmacokinetic.

Appendix 3
Schedule of Anti-Therapeutic Antibody Activities

Visit	Timepoint	Sample Type
Baseline (Day –14)	NA	Pertuzumab ATA (serum)
Day 1 of Cycle 4	Prior to the first infusion	Pertuzumab ATA (serum)
Day 1 of Cycles 10 and 15	Prior to the first infusion	Pertuzumab ATA (serum)
Treatment completion/ discontinuation visit (28 days after the last dose of study treatment)	NA	Pertuzumab ATA (serum)
Follow-up visit (60–90 days after the last dose of study treatment)	NA	Pertuzumab ATA (serum)

ATA = anti-therapeutic antibody; NA = not applicable.

Appendix 4
Response Evaluation Criteria in Solid Tumors: 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 et al. 2009.
[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:
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:
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 be considered measurable only when they are superficial and ≥ 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, <u>if not, the patient should be considered not evaluable from that point forward</u>. 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 ≥ 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 during the study (nadir) with inclusion of baseline

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

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

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

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum during the 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 during the study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR 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:
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. Although 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
- 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 studies 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. Although 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 CR. 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 only non-measurable (therefore non–target) disease, Table 2 is to be used.

Appendix 4
Response Evaluation Criteria in Solid Tumors: 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; SD = stable disease.

[a] "Non-CR/non-PD" is preferred over "SD" for non–target disease since SD is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "SD" 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.

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.

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

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 Table 1, Table 2, and Table 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 CR if the primary tumor is still present but not evaluated as a target or non–target lesion.

Appendix 5
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

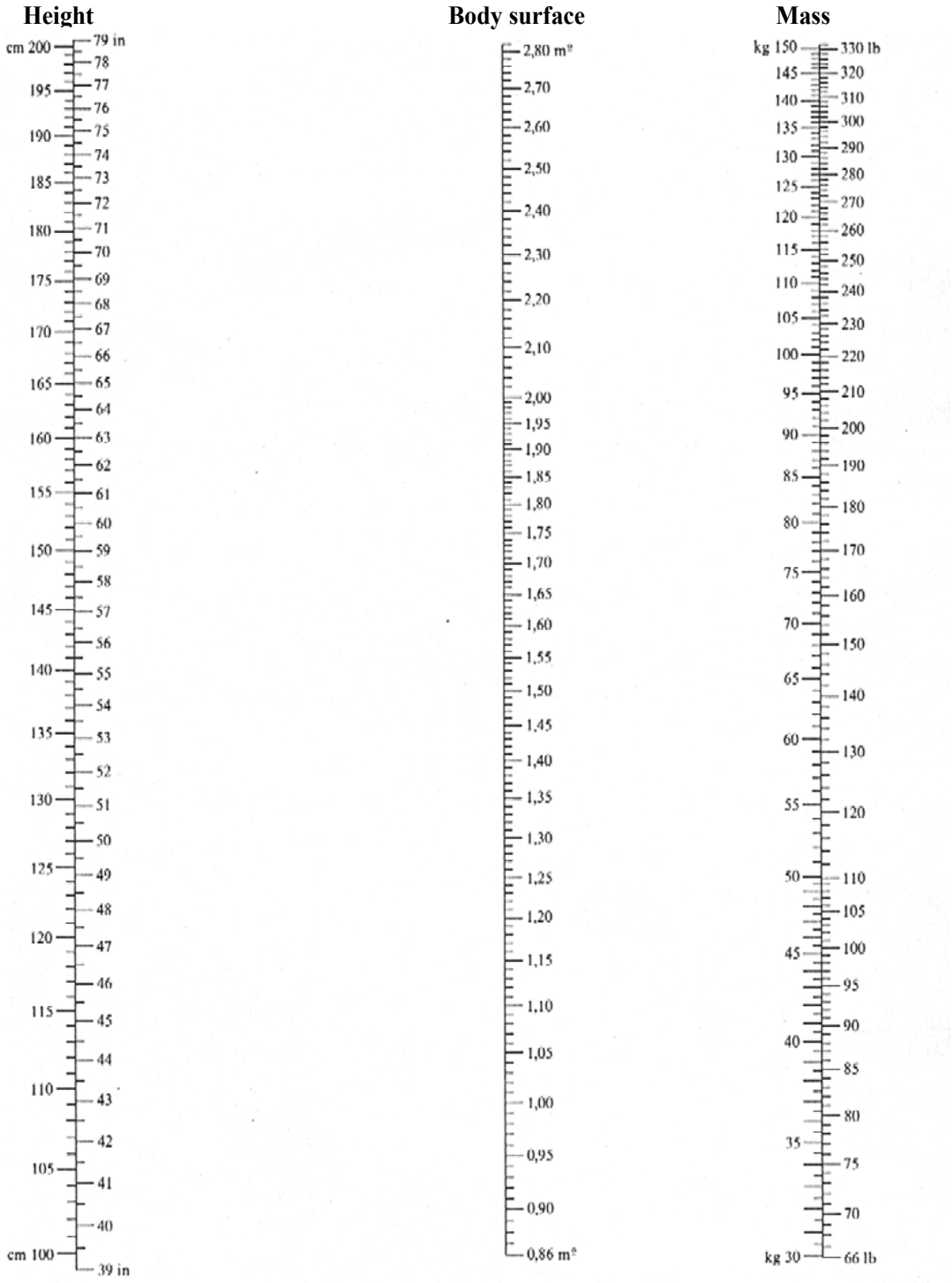
Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but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

Appendix 6
New York Heart Association Functional Classification System for Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Little, Brown & Co, 1994:25.

Appendix 7
Nomogram for 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]

Appendix 8
Standardized Guideline for Surgical Sampling following Neoadjuvant Therapy

DETERMINATION OF LESION (TUMOR OR TUMOR BED) LOCATION

SAMPLE CATEGORIZATION

- Sample with prespecified positioning is defined as a sample obtained from a lesion that has been clearly positioned using skin tattoo or metal clip before neoadjuvant therapy
- Sample without prespecified positioning is defined as either a sample from a lesion that has prespecified but unqualified positioning or a sample without any positioning marker, as follows:

  a) Sample with prespecified but unqualified positioning is defined as a sample obtained from a lesion that has not been clearly positioned before neoadjuvant therapy but is positioned before surgery

  b) Sample without any positioning marker is defined as a sample obtained from a lesion that is clearly positioned neither before neoadjuvant therapy nor before surgery

The table below is intended to provide reference for pathologists when determining lesion location.

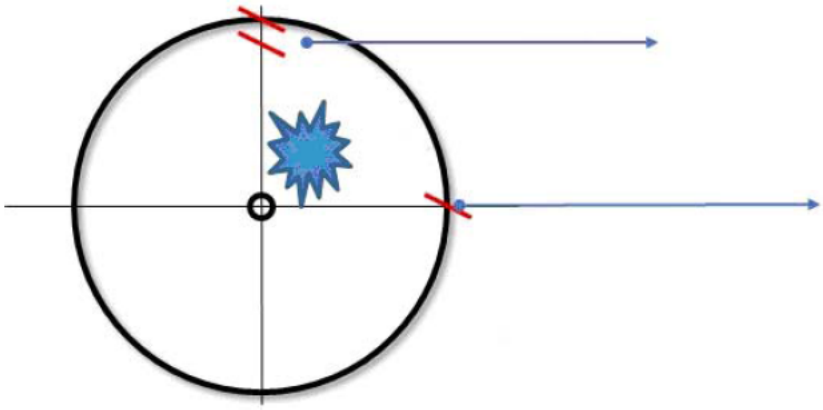
	(Modified) Radical Surgery	Breast-Preserving Surgery
Prespecified positioning • Skin tattoo • Metal clip and others	Mark corresponding area	Identify according to surgical markers
Without prespecified positioning: • Positioning before surgery only • No any positioning	1. Identify quadrant according to anatomical marker grossly on the sample 2. Look for quadrant where the mass is located as recorded at clinical diagnosis 3. Identify in that quadrant	Identify according to surgical markers

SURGICAL MARKERS

- Applicable for breast-preserving surgery
- Method: use markers on two different spots (an example is shown in the figure below; positioning should be determined by clinicians and pathologists on a case-by-case basis in individual center)

Appendix 8
Standardized Guideline for Surgical Sampling following Neoadjuvant Therapy (cont.)

Figure 1 Surgical Marker Example



MEASUREMENT OF LESION (TUMOR OR TUMOR BED) SIZE

Carefully identify the lesion and measure the size of the tumor or tumor bed on three diameters:

- Sample with prespecified positioning: Carefully identify the lesion beneath the markers and measure the size of the tumor or tumor bed on three diameters.
- Sample with prespecified but unqualified positioning: Carefully identify the lesion in corresponding quadrant (see "Surgical markers" above for the positioning of quadrant, the same below) and measure the size of the tumor or tumor bed on three diameters.
- Sample without any positioning marker: Carefully identify the quadrant where the lesion is located and measure the size of the tumor or tumor bed on three diameters.

RESECTION OF TISSUE SAMPLE

BREAST TISSUE

- Sample with prespecified positioning: Obtain sample from breast tissue corresponding to the prespecified markers (such as skin tattoo). Make an incision every 1 cm along the long axis of the breast tissue and cut the sample into several blocks of tissue. At least one piece of sample must be obtained from each block. For example, at least five samples must be obtained from a 5-cm tissue.
- Sample with prespecified but unqualified positioning and sample without any positioning marker: Sample should be carefully obtained from corresponding quadrant where the primary mass is located.

Appendix 8
Standardized Guideline for Surgical Sampling following Neoadjuvant Therapy (cont.)

1. Sample with significant mass: Make an incision every 1 cm along the long axis of the sample and cut it into several blocks of tissue. At least one piece of sample should be obtained from each block. For example, at least five samples must be obtained from a 5-cm tissue.
    a) In case of microscopic non-pathologic complete response (pCR), no additional sampling is required
    b) In case of microscopic pCR, obtain sample from the entire quadrant (in case of breast-preserving surgery, obtain sample from the entire breast tissue)
2. Sample with insignificant mass but fibrotic tumor bed: Obtain sample from fibrotic tumor bed using methods described above.
    a) In case of microscopic non-pCR, no additional sampling is required
    b) In case of microscopic pCR, obtain sample from the entire quadrant (in case of breast-preserving surgery, obtain sample from the entire breast tissue)
3. Sample without significant mass or fibrotic tumor bed: Obtain sample from the entire area beneath the markers (in case of breast-preserving surgery, obtain sample from the entire breast tissue).

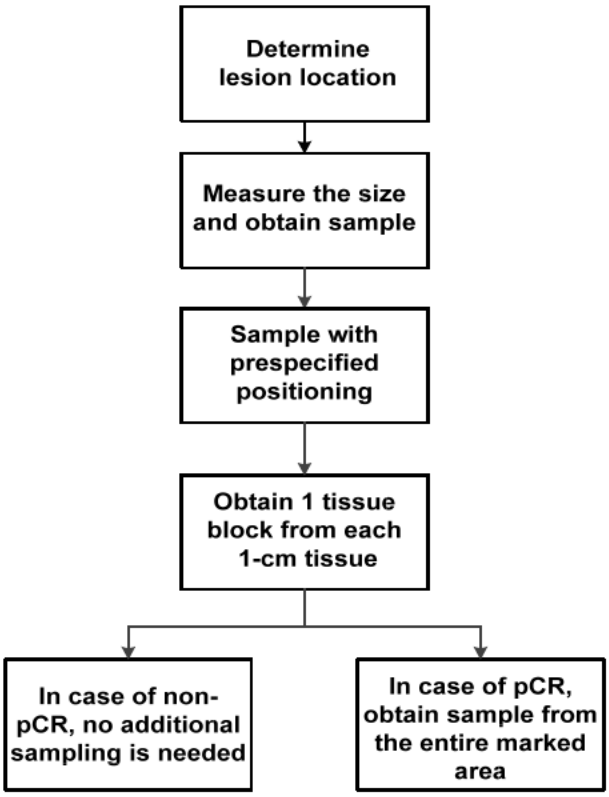
LYMPH NODES

- Rigorously examine the axillary adipose tissue for lymph nodes.
- Section along the longest axis of the lymph nodes.
- Submit a cross section of the largest dimension for histologic evaluation with adjacent connective tissue.

All identified axillary lymph nodes should be sent for histologic examination.

This sampling guideline is intended to provide standards for postoperative sampling procedures following neoadjuvant therapy only.

Appendix 9
Flowchart for Breast Tissue Sampling



pCR = pathologic complete response.
Note: See Appendix 8.