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**

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Pertuzumab (RO4368451)

VERSION NUMBER: 1

IND NUMBER: [redacted]

Eudract Number: [redacted]

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	05-Jul-2017 16:30:35

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF APPENDICES

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study YO28762, “PEONY”.

2. 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) human epidermal growth factor receptor 2 (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 in mainland China, Korea, Taiwan, and Thailand, 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-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:

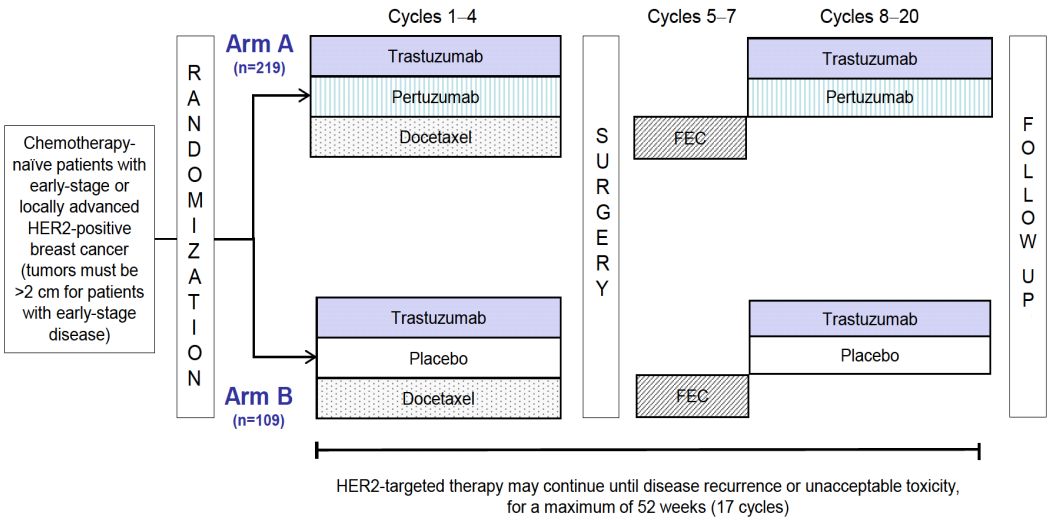
- Arm A
  Trastuzumab (8-mg/kg loading dose for Cycle 8, followed by 6 mg/kg for Cycles 9−20)
  Pertuzumab (840-mg loading dose for Cycle 8, followed by 420 mg for Cycles 9−20)

- 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 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 are evaluated for clinical response prior to surgery (i.e., during Cycles 1−4) in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Patients are 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 their surgical treatment with the assessment of pathological response. Patients are evaluated for safety throughout the study with laboratory tests and adverse event reports. Serum samples are collected from a subset of approximately 50 Chinese patients for characterization of pertuzumab pharmacokinetics.

The pathologic response is evaluated by a local pathologist as well as an Independent Review Committee (IRC) consisting of three external independent pathologists.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Activities in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measure is the total pathologic complete response (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.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- tpCR assessed by a local pathologist
- Breast pathologic complete response (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
- Event-free survival (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

- Disease-free survival (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 (OS) defined as the time from randomization to death from any cause.

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory outcome measures for this study are as follows:

- To explore relationships between pathology findings from the sentinel lymph node biopsy tissue sample, if the biopsy is performed, and the axillary lymph node dissection tissue sampled obtained during the surgery undertaken after neoadjuvant treatment
- Observed pertuzumab concentrations at all specified pharmacokinetic (PK) sampling timepoints
- Observed pertuzumab concentrations compared with concentrations in 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 assess the effect of HER2 extracellular domain (ECD) on PK of pertuzumab
- Incidence of anti-therapeutic antibodies (ATAs) and relationship with PK, safety, and efficacy outcome measures (as data allow)
- tpCR in relation to clinical response, EFS, DFS, and OS.

2.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows:

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

- Laboratory test result abnormalities.

2.3 DETERMINATION OF SAMPLE SIZE

A total of 328 patients have been planned to 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.

2.4 INTERIM AND FINAL ANALYSIS TIMING

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 OS will be performed at the end of the study, approximately 5 years after randomization of the last patient.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients are randomized in a 2:1 ratio to one of the two treatment arms (pertuzumab or placebo) with use of the interactive voice/web−based response system (IxRS). Patients are 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.

3.2 INDEPENDENT REVIEW COMMITTEE

An IRC that consists of independent experts who are not involved in the study (including three pathologists) is used to evaluate the pathologic response.

Details of the composition, roles, and responsibilities of the IRC have been provided in the IRC charter.

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

3.3 SAFETY DATA REVIEW

The Sponsor’s study team has been reviewing AEs, SAEs, and any other safety data in the study on a regularly scheduled basis.

The study team is responsible for reviewing accumulating safety data, assessing and monitoring ongoing safety of patients, evaluating potential changes to the clinical study protocol, and ultimately safeguarding patient safety.

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol YO28762 for the purposes of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients, whether or not the patient received the assigned treatment. The ITT patients will be analyzed according to the treatment assigned at randomization by IxRS.

4.1.2 Pharmacokinetic-Evaluable Population

Pharmacokinetic analyses will be based on PK observations from all patients who received pertuzumab treatment with at least one evaluable post-dose PK sample.

4.1.3 Safety Population

The safety population is defined as patients who receive any amount of study treatment. Patients who receive any amount of pertuzumab will be analyzed as part of treatment Arm A, even if pertuzumab was given in error. Patients who are randomized to the study but who do not receive any study drug will not be included in the safety population.

4.2 DEFINITION OF TREATMENT PERIODS

The concept of the treatment period will be used to define how study data will be reported. For example, typically tables of AEs will be of interest for the period that patients are considered to be on study treatment. This study has a neoadjuvant, adjuvant and treatment–free follow up period. The overall treatment period is defined as the combination of neoadjuvant and adjuvant periods. It will be assumed that patients who have not withdrawn from study treatment according to the database are still in the treatment period.

4.2.1 Neoadjuvant study treatment period

The neoadjuvant study treatment (or “neoadjuvant treatment”) period begins after randomization upon receiving the first dose >0 of any of the neoadjuvant study medications (trastuzumab, pertuzumab, docetaxel), i.e. on Study Day 1.

It ends either:

(i). Immediately before receiving the first dose of adjuvant study treatment (see below); or

(ii). 42 days after the last dose >0 of neoadjuvant study treatment, for patients who discontinued without undergoing primary surgery and never start adjuvant study treatment; or

(iii).42 days after the last dose > 0 of neoadjuvant study treatment or on the day of primary surgery, whichever is later, for patients who undergo primary surgery and discontinued without starting adjuvant study treatment; or

(iv). If a patient has not yet started the adjuvant treatment and has not withdrawn then all assessments will be considered neoadjuvant. In this case the last known date is considered as the end date.

4.2.2 Adjuvant study treatment period

The adjuvant study treatment (or "adjuvant treatment") period begins, after primary surgery, upon receiving the first dose > 0 of any of the five adjuvant treatments (pertuzumab, trastuzumab, 5-Fluorouracil, epirubicin, and cyclophosphamide). It ends 42 days after the last dose of adjuvant study treatment upon treatment completion or discontinuation. If there is no evidence of treatment completion or discontinuation, the patient is considered on treatment.

4.2.3 Overall study treatment period

The overall study treatment period begins after randomization upon receiving the first dose >0 of neo-adjuvant study treatment. It ends either at the end of the neo-adjuvant treatment period as defined in Section 4.2.1, for patients who do not start adjuvant study treatment, or at the end of the adjuvant treatment period as defined in Section 4.2.2.

4.2.4 Treatment-free follow-up

The remaining visits after the on-treatment study periods (see Section 4.2.1 and Section 4.2.2) will take place every 3 months (±28 days) for 1 year, followed by every 6 months (±28 days) thereafter, until disease progression or recurrence or until 5 years after randomization of the last patient, whichever occurs first.

The treatment-free follow-up period is defined to start the day after the end of the overall study treatment period as defined in Section 4.2.3.

4.3 ANALYSIS OF STUDY CONDUCT

Patient enrollment, duration of the follow-up, and the reasons for discontinuation from study periods (neoadjuvant and adjuvant) will be summarized by treatment arm for the ITT population. In addition, major protocol deviations will be summarized by treatment arm.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

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

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

4.5 EFFICACY ANALYSIS

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.

4.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint 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 their 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. The stratification factors will be the same as those used for randomization. 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.

4.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study include 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 OS.

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

The tpCR rate as assessed by the local pathologist will be evaluated using the same methods as those described for the primary efficacy endpoint.

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

The 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 using the same methods as those described for the primary efficacy endpoint.

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

The bpCR rate as assessed by the local pathologist will be evaluated using the same methods as those described for the primary efficacy endpoint.

4.5.2.4 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. Objective response rate 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 the same as those described for the primary efficacy endpoint.

4.5.2.5 Event-Free Survival

The 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.

4.5.2.6 Disease-Free Survival

The 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. So patients are considered to be disease free if they have undergone surgery and no recurrence of disease is reported thereafter. Data from 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 methods for data analysis are the same as those described for EFS.

4.5.2.7 Overall Survival

The OS is defined as the time from randomization to death from any cause. Data from patients 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.

4.5.3 Exploratory Efficacy Endpoints

The relationship between IRC-assessed tpCR and other efficacy endpoints, such as clinical response, EFS, DFS, and OS may be explored when appropriate.

4.5.4 Sensitivity Analyses

The concordance of pathological responses (tpCR and bpCR) between IRC and investigator assessments will be summarized by treatment group.

For some patients, inconsistent values of stratification factors were entered at randomization (i.e., in the IxRS). The stratified analyses of IRC-assessed tpCR and bpCR will be repeated with the values of stratification factors saved in the clinical database.

The primary analysis, comparing tpCR rates among the ITT population, will be repeated only for patients who completed the surgery and have a tpCR assessment available.

The potential impact of herbal remedies on the efficacy, the IRC-assessed tpCR might be explored when appropriate.

4.5.5 Subgroup Analyses

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 the subgroup analyses for IRC-assessed tpCR:

- Age (<65 vs. ≥ 65)
- Region (Mainland of China vs other)
- Menopausal status at randomization (post-menopausal vs pre-menopausal)
- Primary tumor stage at baseline (T2 vs T3 or larger)
- Lymph nodes status at baseline (positive vs negative)

- Histological subtype at baseline (ductal vs non-ductal, not including unknown values)
- Disease category at baseline (early-stage vs locally advanced)
- Hormone receptor status at baseline (positive for ER and/or PgR vs negative for both)
- HER2 subgroups defined as IHC3+ (regardless of FISH status), IHC2+/FISH+ and IHC0/1+/FISH+
- Pathological tumor stage at surgery (T0 or Tis vs T1 or larger)
- Targeted surgery type (breast conserving vs total mastectomy).

The tpCR will be analyzed separately for each subgroup defined by the above variable in a similar way as done for the primary analysis, except that unstratified instead of stratified Cochran-Mantel-Haenszel test will be performed.

4.6 PHARMACOKINETIC ANALYSES

Pharmacokinetic parameters C_{max} and C_{min} values will be tabulated and summarized for pertuzumab at each specified sampling timepoint. Descriptive statistics will include mean, SD, median, 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 PK in the neoadjuvant and adjuvant phase in this study. Additionally, observed serum pertuzumab PK in this study will also be compared with the observed serum pertuzumab PK 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 soluble systemic HER2 ECD and the PK of pertuzumab.

4.7 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, when all patients have completed the treatment completion or study discontinuation visit, and at the final analyses.

4.7.1 Exposure of Study Medication

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

each treatment cycle will be presented for pertuzumab (or placebo), trastuzumab, and chemotherapy by treatment period (neoadjuvant and adjuvant, if applicable).

4.7.2 Adverse Events

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. All AEs 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 Version 4.0. In addition, AEs leading to discontinuation of study treatment and AEs observed on the day of and during the infusion will be summarized by treatment arm. The maximum severity recorded for each AE will be used in the summaries.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

AE summaries will be presented by treatment period (neoadjuvant, adjuvant, overall and follow-up).

4.7.3 Cardiac Safety

The primary cardiac event is defined as heart failure (NYHA III or NYHA IV) and a drop in LVEF of at least 10 ejection fraction points from baseline and to below 50%.

The secondary cardiac event is defined as an asymptomatic or mildly symptomatic (NYHA Class II) drop in LVEF by MUGA scan or echocardiogram confirmed by a second LVEF assessment within approximately 3 weeks showing also a documented drop. A significant LVEF drop is defined as an absolute decrease of at least 10 points below the baseline measurement and to below 50%.

The assessment of the secondary cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease. Therefore, any asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF should be confirmed within approximately 3 weeks, even during follow-up.

Secondary cardiac events will only be counted for patients with no primary cardiac event.

Comparison of incidence of each of the primary and secondary cardiac events by arm will be made by summarizing the proportions in each arm and the difference in proportions with 95% CI using Hauck-Anderson correction.

The composite primary and secondary cardiac endpoint over time with competing risk of non-cardiac death will be compared between treatment groups by Gray's test (Kalbfleisch and Prentice, 2002).

LVEF data analyses will include the following:

The baseline LVEF value and the maximum absolute decrease (or minimum absolute increase if patients' post-baseline LVEF measures are all larger than the baseline value) in LVEF measure from baseline will be summarized. The 95% two-sided confidence limits for the maximum absolute decrease in LVEF measure and the difference between the two treatment arms will be presented. LVEF measurements and change in LVEF from baseline will be summarized by treatment arm and time point in graphical and tabular format.

In addition, LVEF will be summarized by presenting frequencies over time by treatment group for the following categories:

- Increase or no change in Ejection Fraction (EF)
- Decrease from baseline <10 EF points
- Absolute value ≥50% and decrease from baseline ≥10 EF points
- Absolute value < 50% and decrease from baseline ≥ 15 percentage points
- Absolute value < 50% and decrease from baseline ≥ 10 percentage points.

The number and percentage of patients with symptomatic LVSD (heart failure) at any time during the study will be summarized by treatment arm. Symptomatic LVSD (heart failure) will be evaluated by the assessment of NCI CTCAE v4.0 and NYHA class (NYHA II, III and IV).

Risk factors for cardiac dysfunction may be investigated as an exploratory analysis.

Cardiac safety summaries will be presented by treatment period (neoadjuvant, adjuvant, overall, and follow-up).

4.7.4 Laboratory Data

Clinical laboratory tests are 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.

4.7.5 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time including change from baseline. Baseline is defined as the measurement obtained on Cycle 1, Day 1 prior to first dose of study drug.

ECOG performance status will also be summarized over time.

4.8 MISSING DATA

Please refer to Section 4.5.1 and 4.5.2 for methods of handling missing data for the primary and secondary endpoints.

4.9 EXPLORATORY ANALYSES

4.9.1 Biomarker Analyses

The correlation between baseline molecular biomarkers and efficacy outcomes will be evaluated. Biomarkers may include but are not limited to HER2/3 mRNA and/or protein, PIK3CA, phosphatase and tensin homolog (PTEN), programmed death−ligand 1 (PD−L1), and cluster of differentiation 8 (CD8), HER ligands, HER2 extracellular domain (ECD), and other markers that are relevant to breast cancer. 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.

4.9.2 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 (as data allow).

5. REFERENCE

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data; 2nd edition, Chapter 8, John Wiley & Sons, 2002.

Appendix 1
Protocol Synopsis

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 ≥ 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 ≥ 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 ≤ 1
- Completion of all necessary baseline laboratory and radiologic investigations prior to randomization
- Baseline left ventricular ejection fraction (LVEF) ≥ 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.

Appendix 2
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							

		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												
Tumor tissue collection for determination of HER2 status [jj] and exploratory biomarkers (mandatory)	x						x [kk]						

		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 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

1. 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.

2. 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.

3. 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.

[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.