Official Title:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB + HERCEPTIN + DOCETAXEL VERSUS PLACEBO + HERCEPTIN + DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
NCT Number:	**NCT02896855**
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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB+HERCEPTIN+DOCETAXEL VERSUS PLACEBO+HERCEPTIN+DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	YO29296
STUDY DRUG:	Pertuzumab
VERSION NUMBER:	1
IND NUMBER:	Not applicable
EUDRACT NUMBER:	Not applicable
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	28-Mar-2018 06:14:43

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1. BACKGROUND

Study YO29296 ("PUFFIN") is a Phase III, randomized, double-blind, placebo-controlled bridging clinical trial conducted in mainland China. This trial will evaluate the efficacy and safety of pertuzumab+Herceptin+docetaxel versus placebo+Herceptin+docetaxel in Chinese patients with previously untreated human epidermal growth factor 2 (HER2)-positive metastatic breast cancer (MBC).

CLEOPATRA study (Study WO20698), a global Phase III trial, has demonstrated a statistically significant improvement in progression free survival (PFS) in the pertuzumab group compared with the placebo group (hazard ratio [HR]: 0.62; 95% CI: 0.51, 0.75; $p<0.0001$) and an increase in median PFS of 6.1 months (18.5 months in the pertuzumab group versus 12.4 months in the placebo group) (Baselga et al. 2012). The CLEOPATRA study has also shown a statistically significant improvement in overall survival (OS) for the pertuzumab group (HR: 0.68; 95% CI: 0.56, 0.84; $p\leq0.001$). The median OS was 56.5 months in the pertuzumab group compared to 40.8 months in the control group (Swain et al. 2015).

The purpose of Study YO29296 is to evaluate the efficacy and safety of pertuzumab in a randomized, controlled, and comparative setting for Chinese patients with previously untreated HER2-positive MBC.

The purpose of this Statistical Analysis Plan (SAP) is to pre-specify the analyses prior to the database lock for the primary analysis in order to maintain objectivity. The SAP overrides the analyses described in the statistical section of the protocol, as applicable. This document will be approved by the Sponsor prior to the primary analysis. Deviations from this plan will be noted in the Clinical Study Report for Study YO29296.

2. STUDY DESIGN

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

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

Arm A

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

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

Arm B

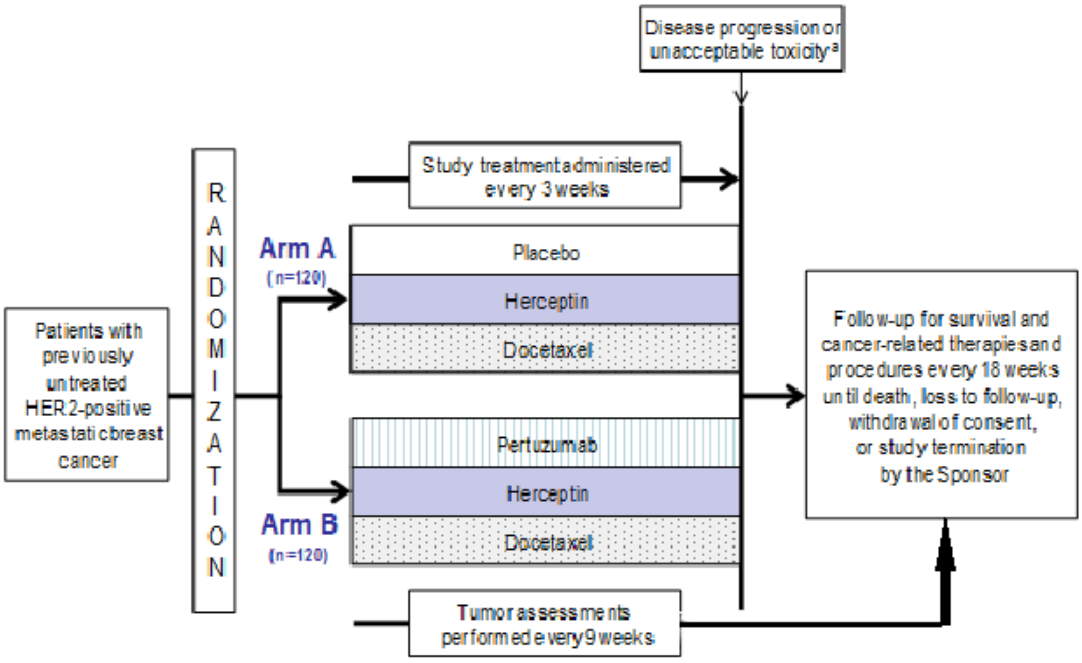
- Pertuzumab (840 mg loading dose for Cycle 1, followed by 420 mg for subsequent cycles), administered by IV infusion every 3 weeks until PD or unacceptable toxicity
- Herceptin (8 mg/kg loading dose for Cycle 1, followed by 6 mg/kg for subsequent cycles), administered by IV infusion every 3 weeks until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

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

Study treatment will be discontinued at the time of PD or unacceptable toxicity, with the possible exception of docetaxel, as described above. Tumor assessments will be performed every 9 weeks from the date of randomization, regardless of treatment delays until PD (see Figure 1). After discontinuation of study treatment, information on survival and cancer-related therapies and medical or surgical procedures will be collected by telephone every 18 weeks until the end of the study, death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

The study design is presented graphically in Figure 1.

Figure 1 Study Schema



HER2=human epidermal growth factor receptor 2.

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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis for Study YO29296 is provided in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 DETERMINATION OF SAMPLE SIZE

The primary objective of Study YO29296 is to assess whether the addition of pertuzumab to the combination of Herceptin and docetaxel prolongs PFS in Chinese patients in a manner consistent with the results from CLEOPATRA study. A consistency threshold is defined as a HR of <0.81, which maintains $\geq 50\%$ of the risk reduction determined in CLEOPATRA study (HR: 0.62).

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

The sample size estimation was based on the following assumptions:

- The median PFS is 11 months in the control arm, with a PFS HR of 0.68.

- The recruitment period is estimated to be 15 months.

2.3 ANALYSIS TIMING

No interim analysis of efficacy is planned. The primary analysis of PFS will be performed after 123 PFS events have occurred, and the required PFS events are expected to be reached at around 23 months after the first patient is enrolled into the study.

3. STUDY CONDUCT

3.1 RANDOMIZATION PROCEDURE

Patients who are eligible for study entry are randomly assigned (1:1) to a treatment arm via the interactive voice or Web-based response system (IxRS) through use of a permuted block randomization scheme.

Randomization procedures use two stratification factors:

- Disease type (visceral disease vs. non-visceral disease) and
- Hormone receptor status (estrogen receptor [ER]- and progesterone receptor [PgR]- negative or ER- and/or PgR-positive).

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population consists of all randomized patients. Patients are assigned to the treatment group to which they were randomized. The ITT population will be used for the primary and secondary efficacy analyses. For objective response, only patients with measurable disease at baseline will be included in the analysis. For duration of response, only patients with an objective response will be included in the analysis.

4.1.2 Safety Population

Safety population will consist of all randomized patients who receive at least one dose of any of the study drugs, with patients grouped according to the treatment actually received, defined by whether at least one dose of pertuzumab was received.

4.2 ANALYSIS OF STUDY CONDUCT

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

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographics and baseline characteristics, such as age, weight, Eastern Cooperative Oncology Group (ECOG) Performance Status, ER/PgR status, HER2 status, prior

treatments for breast cancer, treatment-free interval, and involvement of visceral sites, will be summarized by treatment arm.

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

4.4 EFFICACY ANALYSIS

The emphasis of efficacy analyses is to assess whether the treatment benefit in Chinese patients is consistent with the benefit observed in CLEOPATRA study, thus the hypothesis testing is considered exploratory in this bridging study.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on investigator assessment. PFS is defined as the time from randomization to the first occurrence of progressive disease, as determined by the investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), or death from any cause within 18 weeks after the last tumor assessment, whichever occurs first.

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

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

4.4.2 Secondary Efficacy Endpoints

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

4.4.2.1 Overall Survival

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

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

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

4.4.2.2 Objective Response

Objective response is defined as a complete response or partial response, as determined by the investigator using RECIST v1.1. Only patients with measurable disease at baseline will be included in the analysis of ORR. Patients without a post-baseline tumor assessment will be considered non-responders.

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

4.4.2.3 Duration of Objective Response

Duration of objective response is defined as the time from the first occurrence of a documented objective response to the time of PD, as determined by the investigator using RECIST v1.1, or death from any cause within 18 weeks after the last tumor assessment whichever occurs first. Only patients with an objective response will be included in the analysis. The method for handling censoring is the same as that described for the primary endpoint.

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

4.4.3 Exploratory Efficacy Endpoints

The relationship of biomarkers, such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) status, HER2/3 mRNA, PD-L1, and cluster of differentiation 8 (CD8) expression, with efficacy (response rate, PFS, and OS) may be explored when appropriate.

4.4.4 Sensitivity Analyses

Cox proportional hazards model for PFS will be performed using IxRS-recorded stratification level.

A summary table and Kaplan-Meier plot of the time to censoring in the two treatment arms will be produced to investigate differences in follow-up time. In this analysis, patients who had events in the primary analysis (progressive disease or death within 18 weeks of the last tumor assessment) are censored at the date of their event and patients without an event are regarded as having had an event at the censoring date.

In addition to this, the robustness of the primary analysis will be evaluated through sensitivity analyses:

1. Potential bias introduced by missed visits (If missed two or more consecutive visits before PD, censoring at the last response assessment before PD)
2. Timing of death (including all progression and deaths as an event)
3. Censoring at the time of Next Anti-Cancer Therapy (NACT)

Sensitivity analyses 2 and 3 will be performed as planned. The data associated with sensitivity analysis 1 will be evaluated in the following manner to determine whether this additional sensitivity analysis will need to be performed.

Tabulation of the incidence of PDs identified at a tumor assessment immediately following two or more missing tumor assessment.

If the incidence of these events is minimal (e.g., $<$2% in each treatment group), the sensitivity analysis 1 will be deemed unnecessary.

Other sensitivity analyses not listed here might be explored when appropriate.

4.4.5 Subgroup Analyses

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint, PFS, across important subgroups, forest plots (including estimated hazard ratios) will be provided for the following variables:

- Age-group ($<$65, $\geq$65 years),
- Disease type (stratification factor: visceral disease vs. non-visceral disease),
- Hormone receptor status (stratification factor: ER- and/or PgR-positive versus ER- and PgR-negative),
- ECOG Performance Status,
- Prior treatment status (de novo, adjuvant/neoadjuvant therapy),
- Treatment-free interval ($<$2 years versus $>$2 years vs. no prior therapy),
- HER2 status by central testing (IHC3+ regardless of FISH status, IHC2+/FISH+ and IHC0/1+/FISH+).

If applicable, expanded analyses will be performed using Cox regression models to estimate treatment effect by adjusting covariates in an exploratory manner. Variables to

be considered are the stratification factors as well as other disease- or patient-related prognostic or predictive factors.

4.5 SAFETY ANALYSES

Safety analyses will be performed on the safety population, defined in Section 4.1.2.

4.5.1 Exposure of Study Medication

The numbers of patients who experience any dose interruption, dose modification, or dose discontinuation for any component of the study treatment will be summarized by treatment arm. Descriptive statistics will be presented for total cumulative dose, number of cycles, and number of patients at each treatment cycle.

4.5.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4. All AEs, including serious adverse events (SAEs) that occur on or after the date of the first study drug administration will be summarized by treatment arm and NCI CTCAE grade (v4.0). In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. Adverse events of special interest (AESIs) defined in Section 5.2.3 of the Protocol will be summarized.

For each patient's AE, the maximum severity recorded will be used in the summaries.

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

AE summaries will be presented for overall treatment period and listing for post-treatment follow-up. For the definition of AE reporting period, please refer to Section 5.3.1 of the Protocol.

Separate summaries for adverse events may be provided for the docetaxel period and the period following discontinuation of docetaxel (chemo-free period) as indicated.

4.5.3 Cardiac Safety

Cardiac events (AE and SAEs) will be summarized by SOC Cardiac disorders.

The number and percentage of patients with Symptomatic LVSD at any time during the study will be summarized by treatment arm. Symptomatic LVSD will be evaluated by the assessment of NCI CTCAE v4.0.

SAEs "Cardiac Failure" (using basket SMQ wide "Cardiac Failure") will be summarized as well.

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 $\geq$50% and decrease from baseline $\geq$10 EF points
- Absolute value $<$50% and decrease from baseline $\geq$15 EF points
- Absolute value $<$50% and decrease from baseline $\geq$10 EF points

4.5.4 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Changes in laboratory data will be summarized by grade using NCI CTCAE v4.0 for each treatment arm. Selected abnormal laboratory values, such as worst toxicity grade and toxicity grade shift from baseline, will be summarized by treatment arm.

4.5.5 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.

4.6 MISSING DATA

No values will be imputed for missing data for the primary and secondary efficacy analyses except as specified in Sections 4.4.1 and 4.4.2 for the PFS, OS, and ORR.

4.7 INTERIM ANALYSES

There are no interim analyses planned.

5. REFERENCES

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

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

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PERTUZUMAB + HERCEPTIN + DOCETAXEL VERSUS PLACEBO + HERCEPTIN + DOCETAXEL IN PREVIOUSLY UNTREATED HER2-POSITIVE METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	YO29296
VERSION NUMBER:	3
TEST PRODUCT:	Pertuzumab (RO4368451)
PHASE:	III
INDICATION:	HER2-positive metastatic breast cancer that has not been treated with chemo or biologic therapy
SPONSOR:	F. Hoffmann–La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

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

The secondary efficacy objectives for this study are as follows:

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

Exploratory Objective

The exploratory objective for this study is as follows:

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

Safety Objective

The safety objective for this study is as follows:

- To compare the safety profile between the two treatment arms

Appendix 1
Protocol Synopsis (cont.)

Study Design

Description of Study

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

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

  Patients with measurable or nonmeasurable disease are eligible.

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

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

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

  If the patient is randomized, the same method of LVEF assessment, ECHO or MUGA, must be used throughout the study, and to the extent possible, be obtained at the same institution (see Section 4.5.8). Any prestudy LVEF values obtained during and after Herceptin neoadjuvant or adjuvant treatment will be obtained, as applicable.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1

Appendix 1
Protocol Synopsis (cont.)

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

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

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, and certain non-hormonal intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide
- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 7 months after the last dose of study treatment (Herceptin and/or pertuzumab)

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Negative serum pregnancy test in women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization.
- Able to comply with the study protocol, in the investigator's judgment

Exclusion Criteria

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

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

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

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

Appendix 1
Protocol Synopsis (cont.)

- Current clinical or radiographic evidence of CNS metastases

  A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain is mandatory within 28 days before randomization in cases of clinical suspicion of brain metastases.

- History of exposure to the following cumulative doses of anthracyclines:

  Doxorubicin or liposomal doxorubicin > 360 mg/m^2

  Epirubicin > 720 mg/m^2

  Mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2

  Other anthracycline greater than the equivalent of 360 mg/m^2 of doxorubicin

  If more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

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

  Absolute neutrophil count < 1500 cells/μL

  Platelet count $< 100{,}000$ cells/μL

  Hemoglobin < 9 g/dL

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

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

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

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

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

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

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

  Patients who are known carriers of HBV may be included in the study. Active HBV is defined as presence of each of the following: positive test for hepatitis B surface antigen, detectable levels of HBV DNA, and ALT > ULN.

- Receipt of intravenous (IV) antibiotics for infection within 14 days prior to randomization

Appendix 1
Protocol Synopsis (cont.)

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

Length of Study

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

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

End of Study

The end of the study will occur approximately 3 years after the last patient is enrolled or the trial is terminated by the Sponsor, whichever is earlier.

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

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

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

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

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

Exploratory Outcome Measures

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

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

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence of symptomatic left ventricular systolic dysfunction
- Incidence of asymptomatic LVEF events
- LVEF measurements over the course of the study

Appendix 1
Protocol Synopsis (cont.)

- Incidence and severity of adverse events and serious adverse events NCI CTCAE v 4.0)
- Changes in clinical laboratory results during the study

Investigational Medicinal Products

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

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

- Herceptin (8 mg/kg loading dose for Cycle 1, followed by 6 mg/kg for subsequent cycles)
- Herceptin will be administered until disease progression or unacceptable toxicity.

Test Product

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

Comparator

Patients in Arm A will receive placebo by IV infusion every 3 weeks until disease progression or unacceptable toxicity.

Non-Investigational Medicinal Products

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

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

- Docetaxel (75 mg/m^2)

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

Statistical Methods

Primary Analysis

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

Determination of Sample Size

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

The sample size estimation was based on the following assumptions:

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

Interim Analyses

No interim analysis of efficacy is planned.

Appendix 2
Schedule of Assessments

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

Appendix 2 Schedule of Assessments (cont.)

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

aPTT = activated partial thromboplastin time; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; INR = international normalized ratio; LVEF = left

ventricular ejection fraction; MUGA = multiple-gated acquisition; PET = positron emission tomography; PgR = progesterone receptor; PTT = partial thromboplastin time; Treat. Discon. = Treatment Discontinuation.

[a] Unless otherwise noted, a window of ±3 days will apply to all visits and assessments, except for collection of follow-up survival information, which will have a window of ±7 days.

[b] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

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

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

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

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

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

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

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

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

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

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

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

[n] Tumor assessments will be performed every 9 weeks (±3 days) from the date of randomization until disease progression. If a tumor assessment must be performed early or late, subsequent assessments should be conducted according to the original schedule of every 9 weeks from the date of randomization. All patients should undergo, at a minimum, a chest and abdomen CT or MRI scan. PET scans will not be considered for assessment of efficacy at any time during the study (except as specified for bone scans in the absence of radioactive isotopes).

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

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

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

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

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

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

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

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

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

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

Appendix 2 Schedule of Assessments (cont.)

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

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

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

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

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

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

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